

**NHC-CATALYZED TRANSFORMATIONS: STETTER, BENZOIN, AND RING
EXPANSION REACTIONS**

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By

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ABSTRACT

The thesis begins with an introduction to the world of *N*-heterocyclic carbenes (NHCs) as organocatalyst for the benzoin, Stetter, and extended umpolung transformations. A mini-review outlining the discovery of the reactions, the recent advances, and the current challenges and limitations that remain to be addressed are presented.

Efforts in the introduction of β,γ -unsaturated- α -ketoesters as acceptors for the Stetter reaction are discussed. For the first time, a highly enantioselective intermolecular Stetter reaction is achieved with β -aryl substituted Stetter acceptors (up to >99% ee). Synthetic applications of the Stetter adducts generated from the α -ketoester acceptors are demonstrated to give access to a diverse number of useful building blocks.

The serendipitous discovery of the cross-benzoin reaction with α -ketoester Stetter acceptors has led to the development of the first highly enantio- and regioselective intermolecular cross-benzoin reaction (up to 97% ee). In addition, a highly divergent synthesis of Stetter adducts and cross-benzoin products could be achieved in excellent regioselectivity.

The thesis also includes the development of highly efficient NHC-catalyzed ring expansion reactions to access functionalized lactones and lactams, which are ubiquitous structural features in natural products. The ring expansion of non-strained saturated heterocycles is achieved under mild conditions. It is postulated that a hydrogen bonding interaction between the Breslow intermediate and the conjugate acid of the external base assists the ring-opening step of the transformation. Unactivated prolinal derivatives are

also shown to undergo the ring expansion in a highly efficient manner, thus giving credence to the hydrogen bonding hypothesis.

With the goal of expanding the scope of the reactions in mind, the thesis concludes with proposed future work on the NHC-catalyzed Stetter and cross-benzoin reactions and promising preliminary results are disclosed.

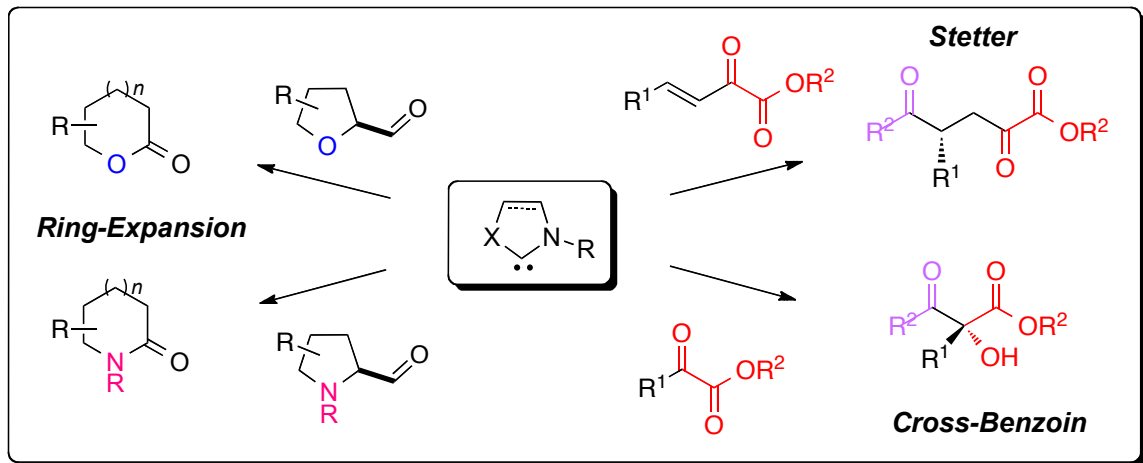


Figure 1.0 NHC-Catalyzed Transformations: Stetter, Cross-Benzoin, and Ring Expansion Reactions.

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TABLE OF CONTENTS

	<u>page</u>
ABSTRACT	iii
ACKNOWLEDGMENTS.....	v
LIST OF TABLES.....	xi
LIST OF FIGURES.....	xii
LIST OF SCHEMES.....	xiii
LIST OF ABBREVIATIONS	xvii
PART I: INTRODUCTION	1
CHAPTER 1: N-HETEROCYCLIC CARBENE-CATALYZED TRANSFORMATIONS	1
1.1 Benzoin and Cross-Benzoin Reactions.....	3
1.2 Stetter Reactions	15
1.3 Extended Umpolung Transformations.....	22
1.4 Conclusion	28
PART II: RESULTS AND DISCUSSION.....	30
CHAPTER 2: NHC-CATALYZED INTERMOLECULAR STETTER REACTION.....	30
2.1 Research Objective	30
2.2 α -Ketoester As Useful Acceptors for the Intermolecular Stetter Reaction	32
2.2.1 <i>Optimization of the Reaction</i>	32
2.2.2 <i>Scope of the Reaction</i>	34
2.2.3 <i>Preliminary Studies on the Extension of the Scope of the Stetter Reaction to Aliphatic Aldehydes</i>	42
2.2.4 <i>Preliminary Studies on the Extension of the Scope of the Stetter Reaction to β-Substituted β,γ-Unsaturated-α-Ketoester Acceptors</i>	45
2.2.5 <i>Synthetic Applications of the Stetter Adducts Obtained with α-Ketoester Acceptors</i>	48
2.3 Conclusion	54
CHAPTER 3: NHC-CATALYZED INTERMOLECULAR CROSS-BENZOIN REACTION.....	56
3.1 Research Objective	56
3.2 α -Ketoesters As Useful Acceptors for the Aldehyde-Ketone Cross-Benzoin Reaction: α -Aryl α -Ketoesters	57

3.2.1	<i>Synthesis of Starting Materials for the Aldehyde-Ketone Cross-Benzoin Reaction</i>	57
3.2.2	<i>Optimization of the Reaction</i>	58
3.2.3	<i>Scope of the Reaction</i>	62
3.2.4	<i>α-Ketoesters as Useful Acceptors for the Aldehyde-Ketone Cross-Benzoin Reaction: Alkyl-, Alkenyl-, and Alkynyl-Substituted α-Ketoesters</i>	67
3.2.5	<i>Preliminary Studies on the Extension of the Scope of the Reaction to Alkyl and Alkenyl α-Ketoester Substrates</i>	68
3.2.6	<i>Synthetic Application of the Cross-Benzoin Product Obtained with α-Ketoester Acceptors & Determination of Absolute Configuration</i>	73
3.3	<i>Conclusion</i>	75
CHAPTER 4: NHC-CATALYZED RING EXPANSION REACTIONS		77
4.1	NHC-Catalyzed Ring Expansion of Tetrahydrofuran Derivatives to Access Lactones	77
4.1.1	<i>Research Objectives</i>	77
4.1.2	<i>Synthesis of Starting Materials</i>	78
4.1.3	<i>Optimization of the Reaction</i>	79
4.1.4	<i>Scope of the Reaction</i>	81
4.2	NHC-Catalyzed Ring Expansion of Prolinal Derivatives to Access Lactams	84
4.2.1	<i>Research Objective</i>	86
4.2.2	<i>Synthesis of Starting Materials</i>	87
4.2.3	<i>Optimization of the Reaction</i>	91
4.2.4	<i>Scope of the Reaction</i>	94
4.3	<i>Conclusion</i>	100
CHAPTER 5: EXPERIMENTAL SECTION		102
5.1	General Methods	102
5.2	Experimental Procedures for the Highly Enantioselective Intermolecular Stetter Reaction	103
	General Procedure for the Preparation of α -Ketoester Stetter Acceptors (43a-k)	103
	Procedure for the Synthesis of β -Alkyl Substituted β,γ -Unsaturated α -Ketoester	106
	General procedure for the NHC-Catalyzed Intermolecular Stetter Reaction	109
	Procedures for the Synthetic Application of the Stetter Adducts to Access Diverse Building Blocks (55, 59, 60, 61, 64-66)	117
5.3	Experimental Procedures for the Highly Enantioselective Intermolecular Cross-Benzoin Reaction	126
	(+)-(S)-5-Isopropyl-2-(perfluorophenyl)-6,8-dihydro-5H-[1,24]triazoleo [3,4-c]oxazin-2-ium tetrafluoroborate (7ah)	126
	Representative procedure for the synthesis on α -ketoester acceptors for the Cross-Benzoin Reaction (68a-d)	129
	Synthesis of Methyl 2-(3-methoxyphenyl)-2-oxoacetate (26e)	130
	Synthesis of Methyl 2-oxo-2-(pyridin-2-yl)acetate (26f)	131
	Synthesis of Methyl 2-oxo-2-(pyridin-3-yl)acetate (26g)	132

General procedure for the NHC-catalyzed cross-benzoin reaction of aliphatic aldehydes and α -ketoesters	133
General procedure for the Reduction of Cross-Benzoin Product 66	147
5.4 Experimental Procedures for the NHC-Catalyzed Ring Expansion for the Synthesis of Functionalized Lactones and Lactams	149
LIST OF REFERENCES.....	207
LIST OF PUBLICATIONS	221
LIST OF NHC PRECATALYSTS.....	222

LIST OF TABLES

<u>Table</u>	<u>page</u>
Table 2-1 Stetter Reaction: Optimization of the Reaction Conditions with Model Acceptor 46a and Furfural 1f	33
Table 2-2 Stetter Reaction: Scope of the Reaction with Model α -Ketoester 43a	35
Table 2-3 Stetter Reaction: Scope of the Reaction with Furfural 1f and Various β -Substituted α -Ketoester Acceptors.....	38
Table 2-4 Stetter Reaction: Scope of the Reaction with Aryl Aldehydes and α -Ketoester Acceptor.	41
Table 2-5 Stetter Reaction: Scope of the Reaction with Aliphatic Aldehydes and α -Aryl α -Ketoester Acceptor 43b	44
Table 2-6 Intermolecular Stetter Reaction with β -Alkyl Substituted β,γ -Unsaturated α -Ketoester Acceptors.....	47
Table 3-1 Optimization of the Enantioselective Aldehyde-Ketone Cross-Benzoin Reaction.	59
Table 3-2 Intermolecular Aldehyde-Ketone Cross-Benzoin Reaction: Scope of the Reaction with Various Alkyl Aliphatic Aldehydes.	63
Table 3-3 Intermolecular Aldehyde-Ketone Cross-Benzoin Reaction: Scope of the Reaction with Hydrocinnamaldehyde.....	66
Table 3-4 Optimization of the Reaction for the Enantioselective Aldehyde-Ketone Cross-Benzoin Reaction using β,γ -Unsaturated- α -Ketoester 69	72
Table 4-1 Ring Expansion of Oxacycloalkane-2-carboxaldehydes: Reaction Optimization with Model Substrate 79a	80
Table 4-2 Ring Expansion of Oxacycloalkane-2-carboxaldehydes: Scope of the Reaction.	82
Table 4-3 Optimization of the Ring Expansion Lactamization Reaction: Base Screening.	93
Table 4-4 Ring Expansion of <i>N</i> -Ts Prolinal Derivatives: Scope of the Reaction.....	96
Table 4-5 Ring Expansion of <i>N</i> -Bn Prolinal Derivatives: Scope of the Reaction.	99

LIST OF FIGURES

<u>Figure</u>	<u>page</u>
Figure 1.0 NHC-Catalyzed Transformations: Stetter, Cross-Benzoin, and Ring Expansion Reactions.....	iv
Figure 1.1 Access to Consonant and Dissonant Connected Compounds through the Coupling of “Natural” and “Unnatural” Synthons.	1
Figure 1.2 Thiazolium-Derived Carbene Catalyst for the Homo-Benzoin Reaction of Benzaldehyde.....	6
Figure 1.3 NHC Precursors for the Homo-Benzoin Reaction.....	7
Figure 1.4 NHC Precatalyst Designs through Steric and Electronic Modulation.....	16
Figure 2.1 Rationale for the Poor Reactivity Observed with Aryl Aldehydes for the Stetter Reaction with β -Substituted Acceptors.....	31
Figure 2.2 Rationale for the Highly Diastereoselective Reduction of the α -Carbonyl of α -Ketoester Substrate 44a using a Closed Chair-like Transition State Model..	52
Figure 2.3 Rationale for the Stereochemical Outcome of the Reduction of the δ -Carbonyl of Stetter Adduct 44a for the Synthesis of Diol 55 using Felkin-Anh Model.....	52
Figure 4.1 Proposed Hydrogen Bonding Interaction Between the Sulfonamide and the Conjugate Acid of <i>i</i> Pr ₂ NEt.	94
Figure 5.1 NOE Experiment for the Determination of the Relative Configuration of 85f	166
Figure 5.2 NOE Experiment for the Determination of the Relative Configuration of 85f'	167
Figure 5.3 NOE Experiment for the Determination of the Relative Configuration of 85g	169
Figure 5.4 NOE Experiment for the Determination of the Relative Configuration of 85g'	170

LIST OF SCHEMES

<u>Scheme</u>	<u>page</u>
Scheme 1.1 Umpolung Reactivity of Aldehydes through the Generation of Dithiane and Cyanohydrin Compounds	2
Scheme 1.2 Wöhler and Liebig's Benzoin Reaction Catalyzed by Cyanide	3
Scheme 1.3 Ukai and Coworkers' Benzoin Reaction Facilitated by Naturally Occurring Thiamin.....	3
Scheme 1.4 Catalytic Cycle for the NHC-Catalyzed Benzoin Reaction Proposed by Breslow.....	4
Scheme 1.5 NHC-Catalyzed Cross-Benzoin Reaction.....	7
Scheme 1.6 Intramolecular Cross-Benzoin Macrocyclization of Dialdehydes.....	8
Scheme 1.7 Scheidt's Use of <i>O</i> -Silyl Thiazolium Carbinols for the Chemoselective Cross-Benzoin Reaction.	9
Scheme 1.8 The Importance of the <i>Ortho</i> -Substituent on Benzaldehydes on the Chemoselectivity of the Cross Aryl and Aliphatic Aldehyde Benzoin Reaction..	10
Scheme 1.9 Substrate and Catalyst Controlled Chemo- and Enantioselective Cross-Benzoin Reaction.....	11
Scheme 1.10 The Formal Cross-Benzoin Reaction between Hydrocinnamaldehyde and Benzaldehyde.....	11
Scheme 1.11 Catalyst Controlled Chemo- and Enantioselective Cross-Benzoin Reaction.....	12
Scheme 1.12 Highly Diastereoselective Intramolecular Aldehyde-Ketone Benzoin Cyclization.....	13
Scheme 1.13 NHC-Catalyzed Desymmetrization of 1,3-Diketones to Access α -Hydroxy Bicyclic Ketones.....	13
Scheme 1.14 Application of the Intramolecular Aldehyde-Ketone Cross-Benzoin Reaction for the Synthesis of (–)-Seragakinone A.....	14
Scheme 1.15 Enantioselective Intermolecular Aldehyde-Ketone Cross-Benzoin Reaction.....	14
Scheme 1.16 Chemo- and Enantioselective Aldehyde-Ketone Cross-Benzoin Reaction of α -Ketoesters with Aliphatic Aldehydes.....	15

Scheme 1.17	Stetter Reaction: Addition of an Acyl Anion Equivalent to Electron-Poor Olefins.....	16
Scheme 1.18	NHC Precatalysts for the Stereoselective Intramolecular Stetter Reaction.....	17
Scheme 1.19	NHC-Catalyzed Intramolecular Stetter Reaction for the Generation of All-Carbon Quaternary Stereogenic Centres.....	17
Scheme 1.20	Mechanistic Investigation of the Intramolecular Stetter Reaction and Proposed Mode of Activation of Catechol	18
Scheme 1.21	Recent Advances in the Stereoselective Intermolecular Stetter Reaction.....	19
Scheme 1.22	Recent Advances in the Stereoselective Intermolecular Stetter Reaction. ³⁹⁻⁴²	20
Scheme 1.23	Recent Advances in the Stereoselective Intermolecular Stetter Reaction with Unactivated, Strained Cyclopropanes.....	21
Scheme 1.24	Recent Advances in the Stereoselective Intermolecular Stetter Reaction with Aliphatic Aldehydes.	21
Scheme 1.25	Recent Advances in the Stereoselective Intermolecular Stetter Reaction to Access α -Amino Ester Derivatives.	22
Scheme 1.26	NHC-Catalyzed Annulations of Enals with Carbonyl Electrophiles to Access Functionalized Lactones.....	23
Scheme 1.27	NHC-Catalyzed Internal Redox Esterification of Alkenals and Alkynals.....	24
Scheme 1.28	Proposed Mechanism for the NHC-Catalyzed Ring Opening Reaction of Epoxyaldehydes.....	25
Scheme 1.29	<i>N</i> -Mes Triazolium-Derived Carbene Catalyzed Ring Opening of Formylcyclopropanes.	26
Scheme 1.30	Diastereoselective Protonation of Catalytically Generated Chiral Enolates... ..	26
Scheme 1.31	NHC-Catalyzed Desymmetrization of Meso Diols through α -Elimination.	27
Scheme 1.32	NHC-Catalyzed Ring Expansion of 4-Formyl- β -Lactams to Access Ring-Expanded Spiro Bicyclic Diamine.	28
Scheme 1.33	NHC-Catalyzed Ring-Opening of γ -Epoxy- α,β -unsaturated	

Aldehydes.	28
Scheme 2.1 α -Ketoester Moiety as an Activating Group and a Synthetic Handle.	31
Scheme 2.2 General Synthetic Route to Access γ -Aryl- β,γ -Unsaturated- α -Ketoesters Acceptors.	32
Scheme 2.3 Attempt to Expand the Scope of the Intermolecular Stetter Reaction to Aliphatic Aldehyde.	42
Scheme 2.4 Proposed Intermolecular Stetter Reaction with β -Alkyl β,γ -Unsaturated α -Ketoester Acceptors.	45
Scheme 2.5 Synthetic Routes to Access β -Alkyl Substituted α -Ketoester Acceptors.	46
Scheme 2.6 The Effect of Chiral Mg Complexes as Co-catalysts for the NHC-Catalyzed Stetter Reaction.	48
Scheme 2.7 Synthetic Applications of the Products Obtained from the Enantioselective Intermolecular Stetter Reactions of γ -Aryl- β,γ -Unsaturated- α -Ketoesters.	50
Scheme 2.8 Bode's Proposed Mechanism for the Decarboxylative Condensation of <i>N</i> -Alkylhydroxylamines and α -Ketoacids.	53
Scheme 2.9 Transformation of Stetter Adduct 44a into Amide Derivative 61	53
Scheme 2.10 Derivatization of Stetter Product 44ab to Trisubstituted Furan and Pyrrole Derivatives.	54
Scheme 3.1 Synthetic Route to Access α -Phenyl α -Ketoester Substrates.	57
Scheme 3.2 Importance of the Substituent on the Ester Moiety of the α -Ketoester Substrate Under Optimized Conditions.	62
Scheme 3.3 Proposed NHC-Controlled Highly Chemoselective Cross-Benzoin Reaction.	67
Scheme 3.4 Intermolecular Aldehyde-Ketone Cross-Benzoin Reaction of Aliphatic Aldehydes with Aliphatic α -Ketoester 64b-c , Alkenyl α -Ketoester 43b,n and Alkynyl α -Ketoester 64d	68
Scheme 3.5 The Importance of the Amount of Base in Intermolecular Cross Aldehyde-Ketone Reaction between Aliphatic α -Ketoesters and Aliphatic Aldehydes.	69
Scheme 3.6 Intermolecular Cross-Benzoin Reaction of Hydrocinnamaldehyde with Alkyl α -Ketoester 64b	69

Scheme 3.7	Effect of the R Group on the Ester Moiety of Alkenyl-Substituted α -Ketoesters in the Aldehyde-Ketone Cross-Benzoin Reaction.	70
Scheme 3.8	Highly Catalyst Controlled Regioselectivity for the Intermolecular Stetter and the Aldehyde-Ketone Cross-Benzoin Reaction.	76
Scheme 4.1	Proposed Catalytic Cycle for the NHC-Catalyzed Ring Expansion Reaction to Access Functionalized Lactones.	78
Scheme 4.2	Synthetic Route to Access Substituted Oxacycloalkane-2-carboxaldehydes for the NHC-Catalyzed Ring Expansion Reaction.	79
Scheme 4.3	Preparation of Oxetene Substrate 79m	79
Scheme 4.4	Rovis' NHC-Catalyzed Redox Amidations of α -Functionalized Aldehydes with Amines.	85
Scheme 4.5	Bode's NHC-Catalyzed Redox Amidations of α -Functionalized Aldehydes with Amines.	86
Scheme 4.6	Ring Expansion Reaction of Prolinal Derivatives Nitrogen-Bearing Electron-withdrawing Group.	87
Scheme 4.7	Synthetic Route to <i>N</i> -Ts, <i>N</i> -Ac, and <i>N</i> -Boc Prolinal Substrates.	87
Scheme 4.8	Synthetic Route to <i>N</i> -Benzyl L-Prolinal.	87
Scheme 4.9	General Method to Access Functionalized <i>N</i> -Tosyl Azacycloalkane-2-carboxaldehyde Substrates.	88
Scheme 4.10	Synthetic Pathway to Access (2 <i>S</i> ,4 <i>R</i>)-1-Benzyl-4-(<i>tert</i> -butyl dimethylsilyloxy)pyrrolidine-2-carbaldehyde 93b	89
Scheme 4.11	Synthetic Pathway to Access (2 <i>S</i> ,5 <i>R</i>)-5-Allyl-1-benzylpyrrolidine-2-carbaldehyde 93c	90
Scheme 4.12	Synthetic Pathway to Access <i>N</i> -Benzylazetidine-2-carbaldehyde 91d	91
Scheme 4.13	Synthesis of 1-Benzylpiperidine-2-carbaldehyde.	91
Scheme 4.14	Preliminary Optimized Reaction Conditions Established by Li Wang for the NHC-Catalyzed Ring Expansion Reaction.	91
Scheme 4.15	NHC-Catalyzed Lactamization in the Absence of an External Base.	100

LIST OF ABBREVIATIONS

A	observed optical rotation
$[\alpha]$	specific rotation [in (deg mL)/(g dm)]
Å	angstrom(s)
a	acceptor, a
Ac	acetyl
aq	aqueous
Ar	aryl
Bn	benzyl
Boc	<i>tert</i> -butyloxycarbonyl
<i>t</i> Bu	<i>tert</i> -butyl
°C	degrees Celsius
<i>c</i>	concentration
calcd	calculated
cat.	catalytic
CBz	carboxybenzyl
CI	chemical ionization
conv.	conversion
<i>m</i> CPBA	meta-chloroperoxybenzoic acid
CSA	10-camphorsulfonic acid
δ	chemical shift (in parts per million)
d	donor, doublet (spectral)
DBU	1,8-diazabicycl[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
de	diastereomeric excess
DIAD	diisopropyl azodicarboxylate
diast.	diastereomer

DIBAL-H	diisobutylaluminium hydride
DMAP	4-(dimethylamino)pyridine
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
E	electrophile
ee	enantiomeric excess
EI	electron-ionization
ent	enantiomer
equiv.	equivalent
ESI	electrospray ionization
Et	ethyl
EWG	electron-withdrawing group
FTIR	fourier transform infrared
h	hour(s)
HetAr	heteroaromatic
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IBX	2-iodoxybenzoic acid
<i>J</i>	coupling constant (spectral)
kCal	kilocalories
KHMDS	potassium bis(trimethylsilyl)amide
LiHMDS	lithium bis(trimethylsilyl)amide

lit.	literature
M	molar (moles/L)
m	multiplet (spectral)
$[M]^+$	parent molecular ion
Me	methyl
Mes	mesityl (2,4,6-trimethylphenyl)
min	minute(s)
mmol	millimole(s)
mol	mole(s)
m.p.	melting point
MS	molecular sieves
m/z	mass-to-charge ratio
nd	not determined
NHC	<i>N</i> -heterocyclic carbene
nm	nanometer(s)
nmr	nuclear magnetic resonance
Nu	nucleophile
P	protecting group
PCC	pyridinium chlorochromate
PFPOH	pentafluorophenol
Ph	phenyl
PhH	benzene
PhMe	toluene
PMA	phosphomolybdic acid
PMP	para-methoxyphenyl
ppm	parts per million
PPTS	pyridinium para-toluenesulfonate

<i>i</i> Pr	<i>iso</i> -propyl
<i>n</i> Pr	<i>n</i> -propyl
py	pyridine
q	quartet (spectral)
R _f	retention factor
rt	room temperature
s	singlet (spectral)
t	time; triplet (spectral)
TBAI	<i>tert</i> -butylammonium iodide
TBDMS	<i>tert</i> -butyldimethylsilyl
TBDPS	<i>tert</i> -butyldiphenylsilyl
TES	triethylsilyl
TFA	trifluoroacetic acid
TIPS	triisopropylsilyl
THF	tetrahydrofuran
TLC	thin-layer chromatography
TS	transition state
Ts	tosyl (para-toluenesulfonamide)
v	volume
w	weight

PART I: INTRODUCTION

CHAPTER 1: *N*-HETEROCYCLIC CARBENE-CATALYZED TRANSFORMATIONS

One of the biggest challenges in organic chemistry is the catalytic enantioselective formation of carbon-carbon bonds. The classical mode of reactivity of most organic reactions is polar in nature, where carbon-carbon bonds are created or broken from nucleophilic (donor, d) and electrophilic (acceptor, a) sites. As a result, the formation of carbonyl bearing compounds normally arises from synthons with alternating acceptor and donor reactivity pattern. It is clear from a simple analysis of dicarbonyl compounds “*that molecules with connectivity of alternating charges (consonant relationship) are much easier to synthesize than those in which like charges are placed on adjacent atoms (dissonance connectivity)*” (Figure 1.1).¹ (Hudlický, p. 187)

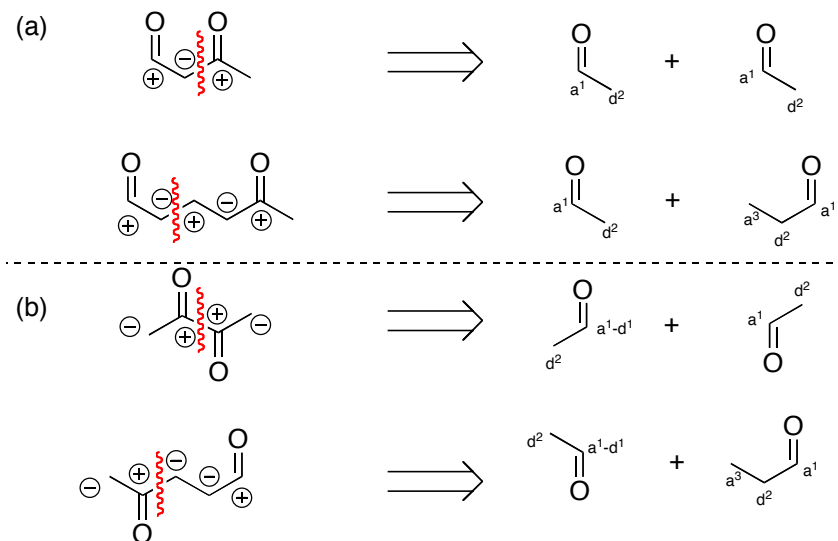
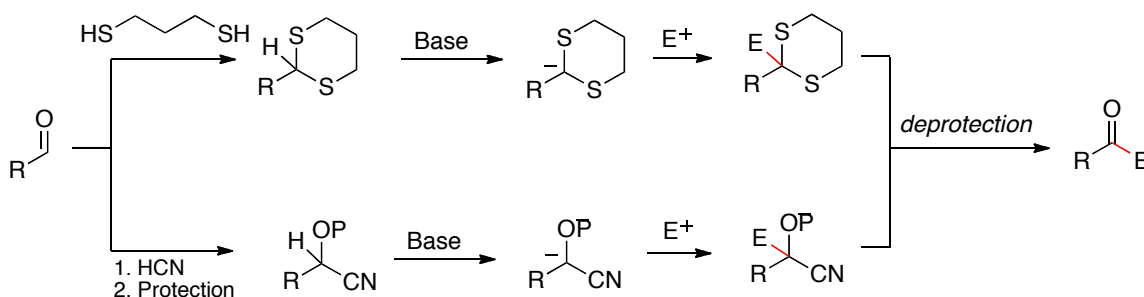


Figure 1.1 Access to Consonant and Dissonant Connected Compounds through the Coupling of “Natural” and “Unnatural” Synthons.

The logical disconnection leading to the formation of 1,3- and 1,5-dicarbonyl molecules reveals the requirement of two carbonyl synthons with a^1+d^2 and a^3+d^2 reactivity (Figure 1.1a). A number of methodologies are available for the synthesis of

these consonantly connected 1,3- and 1,5-difunctionalized molecules; the Michael and aldol reactions are two excellent examples.

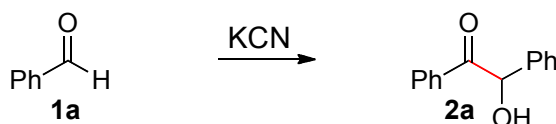
On the contrary, molecules in which like charges are placed on adjacent atoms, also known as dissonantly connected are more difficult to prepare (Figure 1.1b). The disconnection leading to the formation of dissonantly connected compounds bearing 1,2- and 1,4-dicarbonyl functionalities are not straightforward and require the “unnatural” coupling of two components with the same polarity. The inversion of polarity (umpolung) of carbonyl moieties is required to achieve the coupling of two components with the same polarity to access molecules with dissonant connectivity of charges. Seebach and Corey have made pioneering contributions in the coupling of two components with the same polarity.² Two excellent examples of such reactivity are the deprotonation of dithiane and cyanohydrin compounds (Scheme 1.1). Direct, asymmetric catalytic processes that proceed through the inversion of reactivity of carbonyl moieties are of significant value, as they open up new synthetic pathways. In this context, it is not surprising to note the ability to invert the reactivity of aldehydes has attracted much attention.



Scheme 1.1 Umpolung Reactivity of Aldehydes through the Generation of Dithiane and Cyanohydrin Compounds

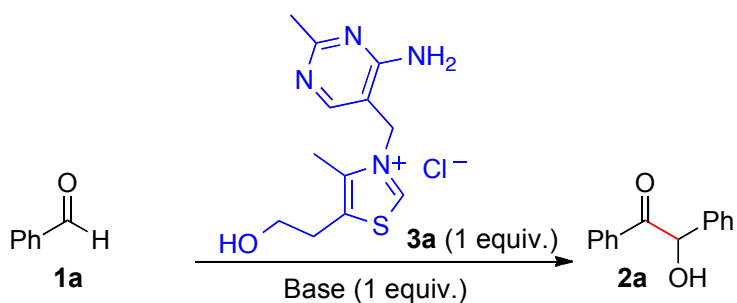
1.1 Benzoin and Cross-Benzoin Reactions

Wöhler and Liebig first discovered the benzoin reaction back in 1832.³ The seminal work on the coupling of aldehydes through a cyanide-catalyzed formation of α -hydroxy carbonyl products (also known as the benzoin reaction) was the first example in which the inversion of the normal mode of polarity of aldehydes was achieved (Scheme 1.2).



Scheme 1.2 Wöhler and Liebig's Benzoin Reaction Catalyzed by Cyanide

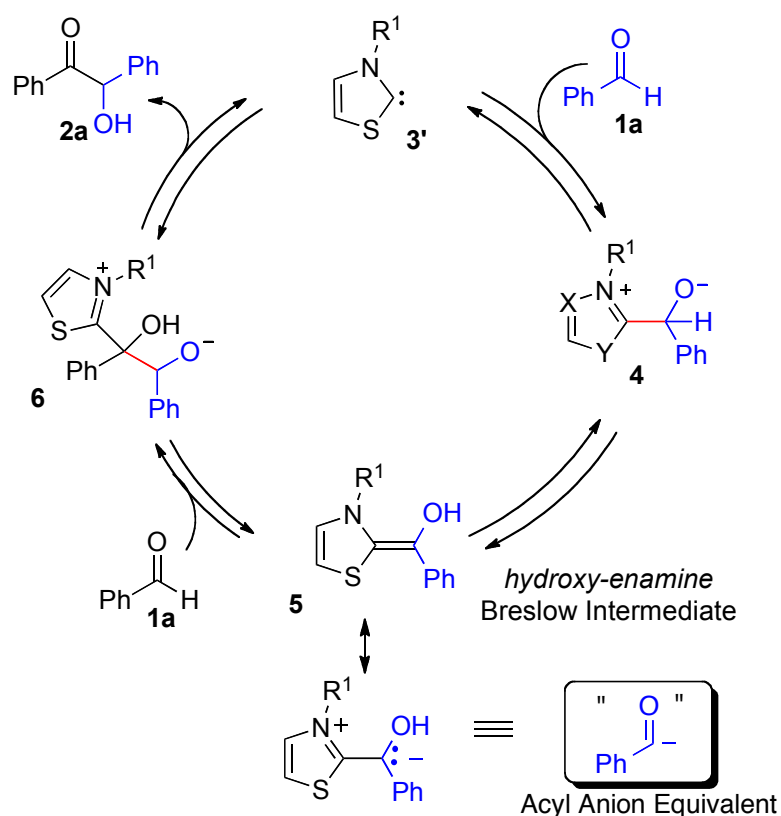
Over 100 years after Wöhler's and Liebig's discovery, Ukai and coworkers found that the same transformation proceeded with a stoichiometric amount of naturally occurring thiamin, in the presence of equal molar concentration of base (Scheme 1.3).⁴ The discovery of this transformation has opened up new synthetic venues in organic synthesis; allowing access to 1,2-difunctionalized, α -hydroxy ketone compounds through C-C bond formation.



Scheme 1.3 Ukai and Coworkers' Benzoin Reaction Facilitated by Naturally Occurring Thiamin.

In 1958, Breslow laid the foundation for the field of *N*-heterocyclic carbene (NHC)-catalysis with his proposed mechanistic model to explain the thiamine-facilitated

benzoin reaction (Scheme 1.4).⁵ The first step of the proposed mechanism is the formation of the catalytic carbene species **3'** by deprotonation of the corresponding thiazolium salt. Subsequent nucleophilic addition of the carbene onto aldehyde **1a**, followed by tautomerization generates the hydroxy-enamine "Breslow" intermediate **5**. The intermediate formed can be seen as an "acyl anion equivalent," for which the resonance structure of the hydroxy-enamine illustrates the effective inversion of reactivity of the electrophilic carbon of the aldehyde to a nucleophilic acylating agent. In the presence of an electrophile, intermediate **5** effects nucleophilic addition and regenerates the carbene catalyst.



Scheme 1.4 Catalytic Cycle for the NHC-Catalyzed Benzoin Reaction Proposed by Breslow.

In addition to the reversal of reactivity (umpolung) of aldehydes and the formation of a new C-C bond, this unique reaction also creates a new stereogenic centre. Furthermore, the α -hydroxy carbonyl moiety generated from the benzoin reaction serves as a highly valuable building block⁶ and is a ubiquitous structural feature found in numerous biologically active compounds and natural products,⁷ making the benzoin reaction a valuable tool in synthetic chemistry.

The first enantioselective intermolecular homo-coupling of benzaldehyde was reported by Sheehan and Hunneman, using chiral thiazolium precatalyst salt **3c** (Figure 1.2).⁸ However, the homo-coupling of benzaldehyde with thiazolium-derived carbene catalysts resulted in poor reactivity and poor enantioselectivity (9% yield, 22% ee). The same group illustrated that increasing the steric bulk on the thiazolium precatalyst around the reactive site of the carbene **3d** significantly enhanced the enantioselectivity of the reaction (6% yield, 52% ee), albeit in low yield.⁹ Despite much effort by various groups in the development of chiral thiazolium precatalysts **3e-k**,¹⁰ no improvements in the enantioselectivity of the reaction could be achieved.

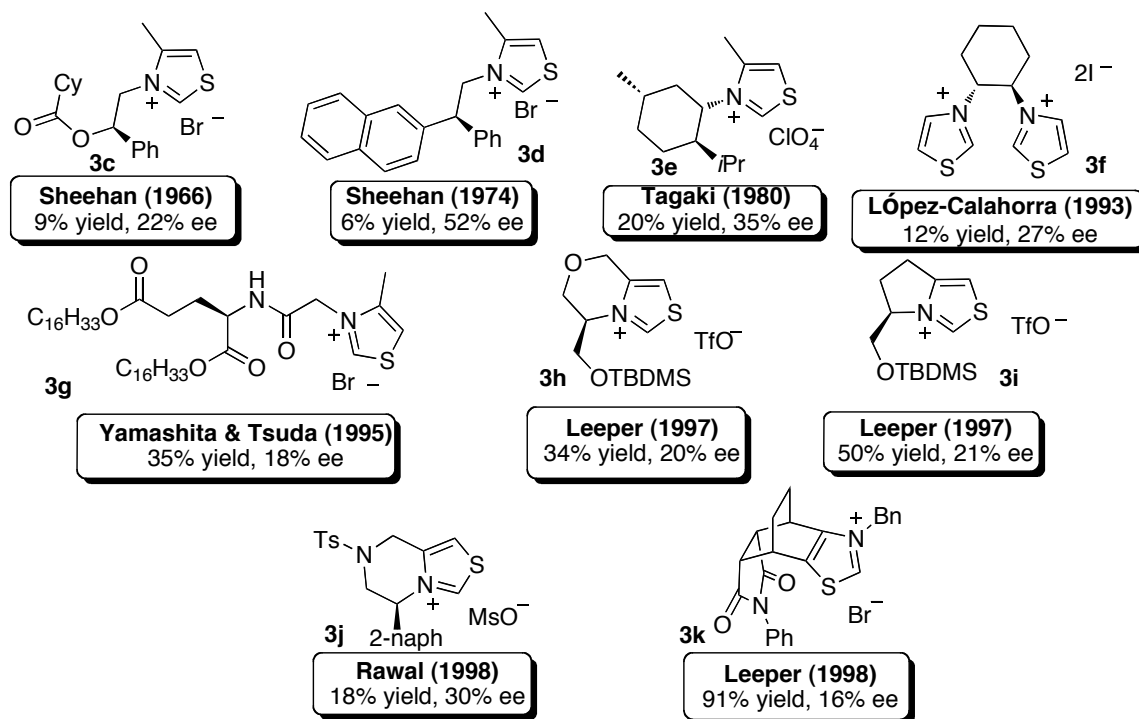


Figure 1.2 Thiazolium-Derived Carbene Catalyst for the Homo-Benzoin Reaction of Benzaldehyde.

A significant breakthrough in the enantioselective intermolecular homo-coupling of aldehydes was achieved through the development of chiral 1,2,4-triazolium precatalysts, pioneered by Enders¹¹ and Leeper (Figure 1.3).¹² Following their work, other chiral triazolium precatalysts were developed for the homo-benzoin reaction, affording excellent enantioselectivity for aromatic aldehydes (up to >99% ee) and lower enantioselectivity for heteroaromatic aldehydes (up to 88% ee) in the benzoin reaction.¹³ Notably, You and coworkers demonstrated the dramatic difference in reactivity and stereoselectivity when varying the counterion of the precatalyst (X = Cl: 95% yield, 95% ee vs. X = PF₆: 81% yield, 86% ee),^{13b} however, the reason behind such difference in reactivity is still unknown.

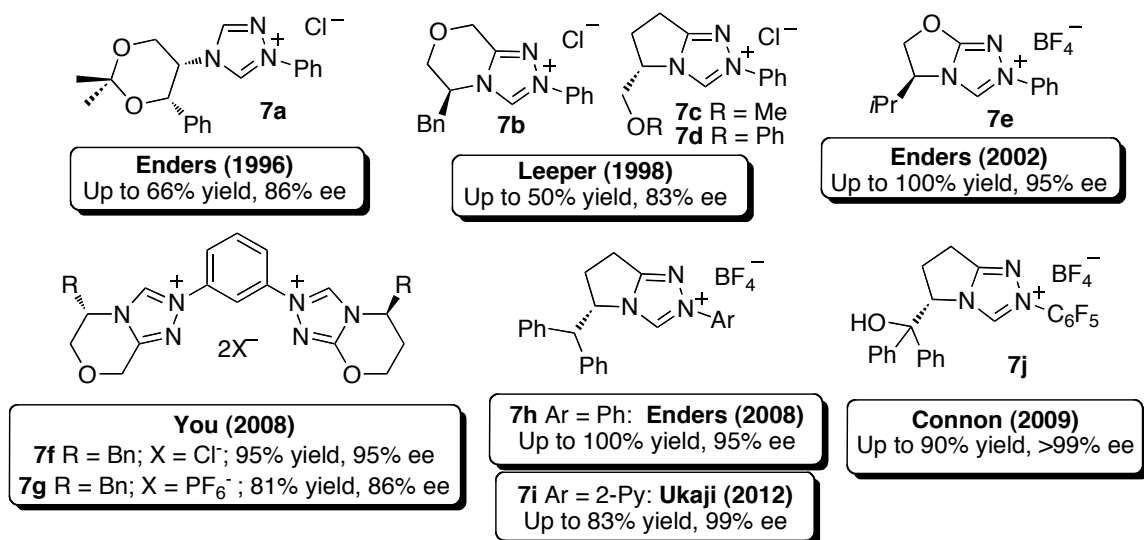
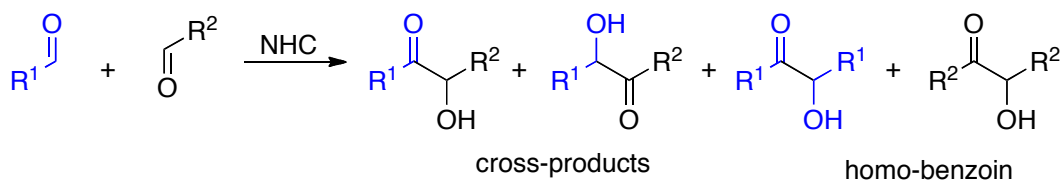


Figure 1.3 NHC Precursors for the Homo-Benzoin Reaction.

The most interesting extension of the benzoin reaction, the chemoselective coupling of two different aldehydes still remains as a significant challenge. Two homo-benzoin and two cross-benzoin products may be formed, with each as two possible enantiomers (Scheme 1.5).

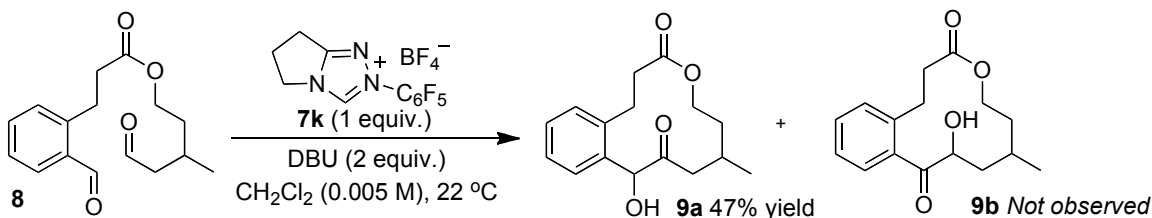


Scheme 1.5 NHC-Catalyzed Cross-Benzoin Reaction.

As the formation of the benzoin product is known to be reversible, thermodynamic control may be used to selectively produce a single cross-benzoin product. Homo-benzoin products have also been used as “masked aldehydes” for the chemoselective aza-benzoin reaction.¹⁴ Although various benzoin products are known to be formed reversibly, Connon and coworkers have shown that the retro-benzoin of products generated from the homo-coupling of sterically-hindered (*o*-substituted

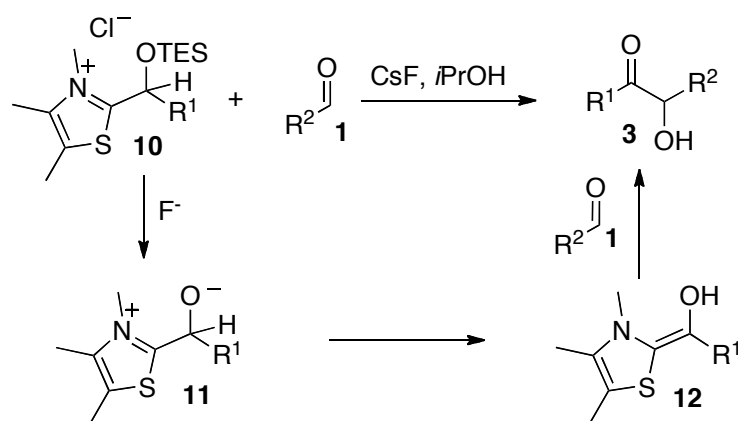
aromatic) aldehydes and aliphatic aldehydes proceeds very slowly or irreversibly through crossover-experiments.¹⁵ Therefore, the nature of the aldehyde plays a critical role in the overall selectivity of the reaction. Another major challenge with the enantioselective cross-benzoin reaction is that the product is susceptible to racemization through base-induced enolization or through a retro-benzoin reaction. Despite the challenges with the cross-benzoin reaction, several groups have found methods to improve the chemoselectivity through substrate and catalyst control.

The first reported intramolecular benzoin coupling of dialdehyde substrates, studied by Cookson and Lane, afforded α -hydroxy cyclopentanone in poor chemoselectivity.¹⁶ Miller's macrocyclization of two electronically different aldehydes afforded good chemoselectivities, albeit in low yields (Scheme 1.6).¹⁷ The origin of the chemoselectivity of the reaction was investigated through control experiments. Slow interconversion of **9b** (obtained through other means) to **9a** was observed at elevated temperatures in the presence of DBU, presumably through the formation of an ene-diol. However, when **9b** was re-subjected to the reaction conditions, **9a** was not observed. The formation of **9a** is presumably a result of kinetic control. Miller et al. suggested that the steric hindrance of *o*-substituted benzaldehyde disfavors the formation of the Breslow intermediate, limiting the role of the aromatic aldehyde to the acceptor in the macrocyclization.



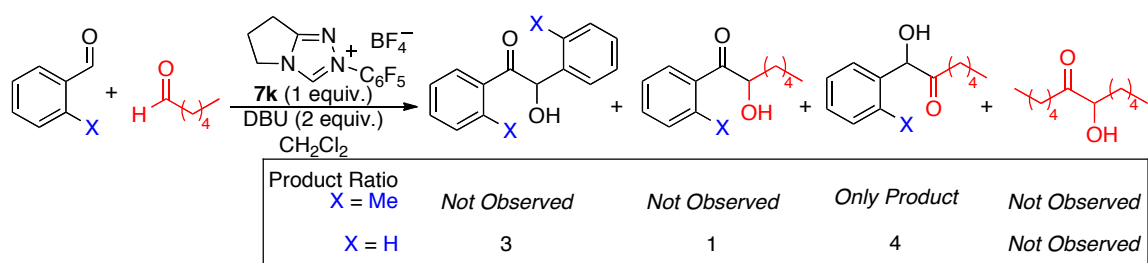
Scheme 1.6 Intramolecular Cross-Benzoin Macrocyclization of Dialdehydes.

The intermolecular cross-coupling of aromatic and aliphatic aldehydes was first reported by Stetter et al. An achiral thiazolium salt and excess amounts of the aliphatic aldehyde afforded good yields of the cross-benzoin product.¹⁸ Scheidt successfully suppressed the formation of homo-benzoin products through the use of *O*-silyl thiazolium carbinol **10** as substrates. This protected ‘Breslow intermediate’ is deprotected in situ using a fluoride source. When the reaction is carried out using a large excess of the corresponding aldehyde (4 equiv.) a single cross-benzoin product is obtained in moderate to good yields (up to 80% yield, Scheme 1.7).¹⁹ Notably, this method gives access to the cross-coupling of two different aliphatic aldehydes, which has yet to be achieved through NHC catalysis.



Scheme 1.7 Scheidt's Use of *O*-Silyl Thiazolium Carbinols for the Chemoselective Cross-Benzoin Reaction.

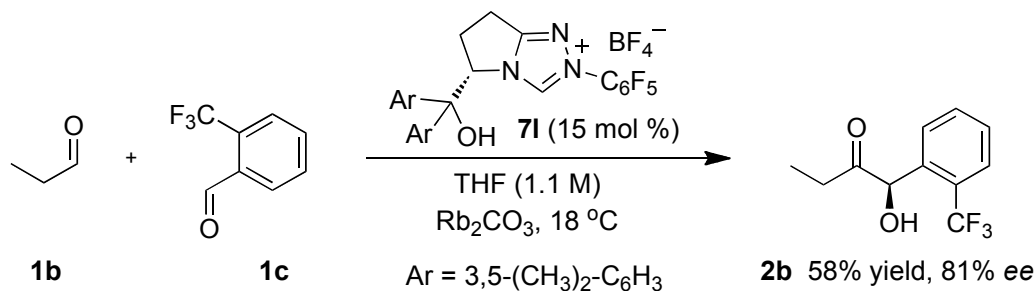
Additionally, Miller and coworkers, have shown in one example that excellent chemoselectivity can be achieved between *o*-tolualdehyde and *n*-hexanal, for which the sole isolable cross-benzoin product was formed from the generation of the ‘acyl anion equivalent’ of the aliphatic aldehyde (Scheme 1.8). In contrast, the use of unsubstituted benzaldehyde resulted in the formation of both possible cross-benzoin products and the homo-benzoin product derived from benzaldehyde.



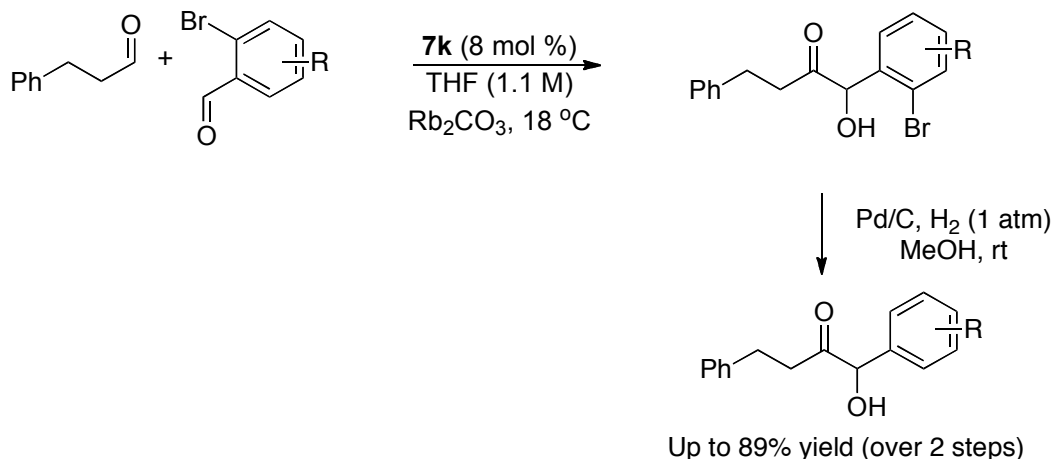
Scheme 1.8 The Importance of the *Ortho*-Substituent on Benzaldehydes on the Chemoselectivity of the Cross Aryl and Aliphatic Aldehyde Benzoin Reaction.

In 2011, following Miller's work, Connon and coworkers reported a highly chemoselective intermolecular cross-benzoin reaction between sterically-hindered *ortho*-substituted benzaldehydes and aliphatic aldehydes using substrate and catalyst control.¹⁵ Use of achiral, electron-deficient triazolium salt **7k** resulted in the formation of the cross-benzoin product in good chemoselectivity. In contrast, the use of achiral thiazolium salt **3b** resulted in the formation of both possible types of cross-benzoin products without chemoselectivity between the two products (1:1). The same group had also shown one stereoselective example of the cross-coupling of aldehydes using chiral triazolium salt **7l**, moderate enantioselectivity of the cross-benzoin product was obtained in excellent chemoselectivity (Scheme 1.9). The size of the *ortho* substituent played a crucial role in controlling the chemoselectivity of the reaction. Excellent chemoselectivity was observed with bromo, methoxy, and trifluoromethyl substituents, whereas a much smaller fluorine atom resulted in poor chemoselectivity. The use of *o*-halogenated benzaldehydes could give access to formal cross-benzoin products with unsubstituted benzaldehydes and aliphatic aldehydes (Scheme 1.10). The chemoselectivity of the reaction was highly temperature-dependent, as cooling from 18 °C to 5 °C resulted in significant decrease in selectivity. The cross-benzoin product formed from the *ortho*-substituted aromatic

aldehyde was found to be formed irreversibly, presumably due to the steric bulk of the ortho-substituent of the aromatic ring.



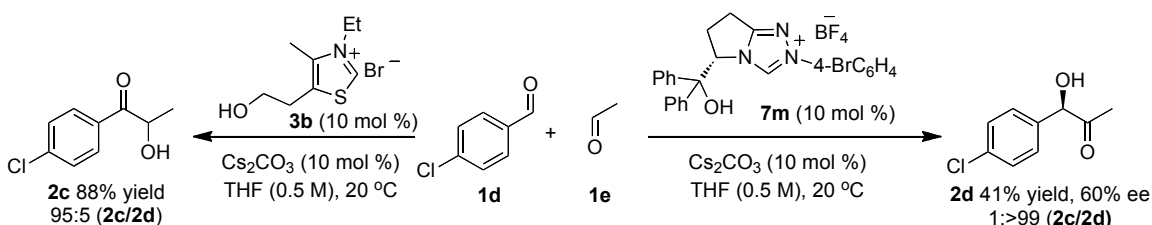
Scheme 1.9 Substrate and Catalyst Controlled Chemo- and Enantioselective Cross-Benzoin Reaction.



Scheme 1.10 The Formal Cross-Benzoin Reaction between Hydrocinnamaldehyde and Benzaldehyde.

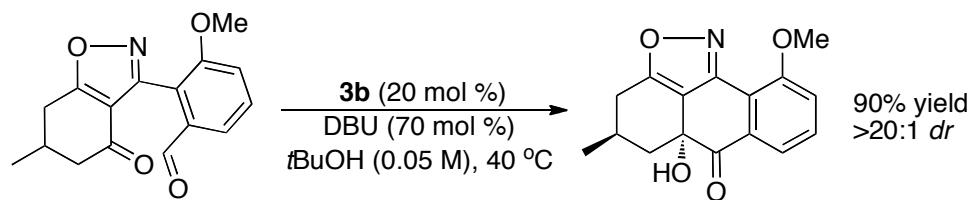
Yang and coworkers reported an interesting catalyst-controlled chemoselective cross-benzoin reaction between *para*-substituted benzaldehydes and acetaldehyde (Scheme 1.11).²⁰ Acetaldehyde is used in large excess (10 equiv.) due to its high volatility, as well as to suppress the formation of the homo-benzoin product resulting from the coupling of aromatic aldehydes. Both cross-benzoin products **2c** and **2d** can be obtained in a regioselective fashion by employing either thiazolium salt **3b** or achiral electron-deficient triazolium salt **7k**, respectively. Moderate enantioselectivity can be achieved with chiral triazolium salt **7m** (60% ee). The origin of the difference in

reactivity between the two families of NHCs is still unknown. However, the difference in steric bulk between the two NHC precatalysts (**3b** vs. **7k**) could be responsible for the dramatic difference in chemoselectivity. On the other hand, the difference in electronic properties of the carbenes cannot be neglected, as electron-deficient aromatic aldehydes result in high chemoselectivity with precatalyst **3b** and electron-rich aromatic aldehydes react chemoselectively with precatalyst **7k**.



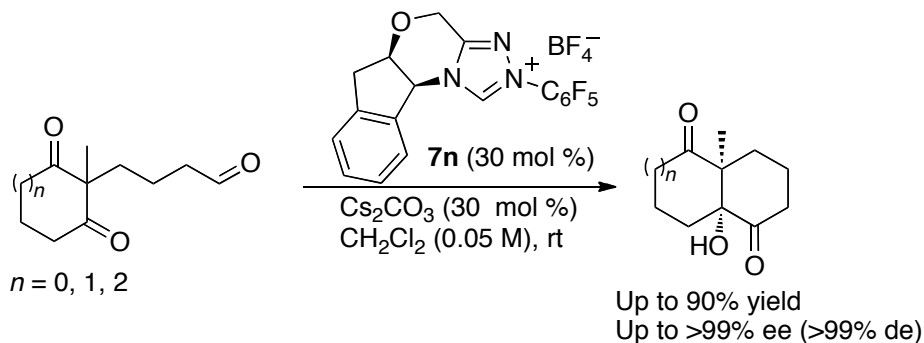
Scheme 1.11 Catalyst Controlled Chemo- and Enantioselective Cross-Benzoin Reaction.

An interesting variation of the benzoin reaction independently pioneered by Enders and Suzuki is the efficient, enantioselective NHC-catalyzed cross-coupling of aldehydes and ketones to access six-membered cyclic α -hydroxy ketones (up to 93% yield and 99% ee).²¹ However, this methodology did not extend well to the synthesis of five-membered rings which were obtained in low enantioselectivity (up to 75% ee).²¹ Furthermore, Suzuki found that excellent diastereoselectivity can be achieved with substrates bearing stereogenic centers when achiral thiazolium precatalyst **3b** was employed (Scheme 1.12).²¹ A competing intermolecular homo-benzoin reaction was also problematic for the transformation to access six-membered rings. This side reaction could effectively be suppressed when the reaction was performed at low concentrations.



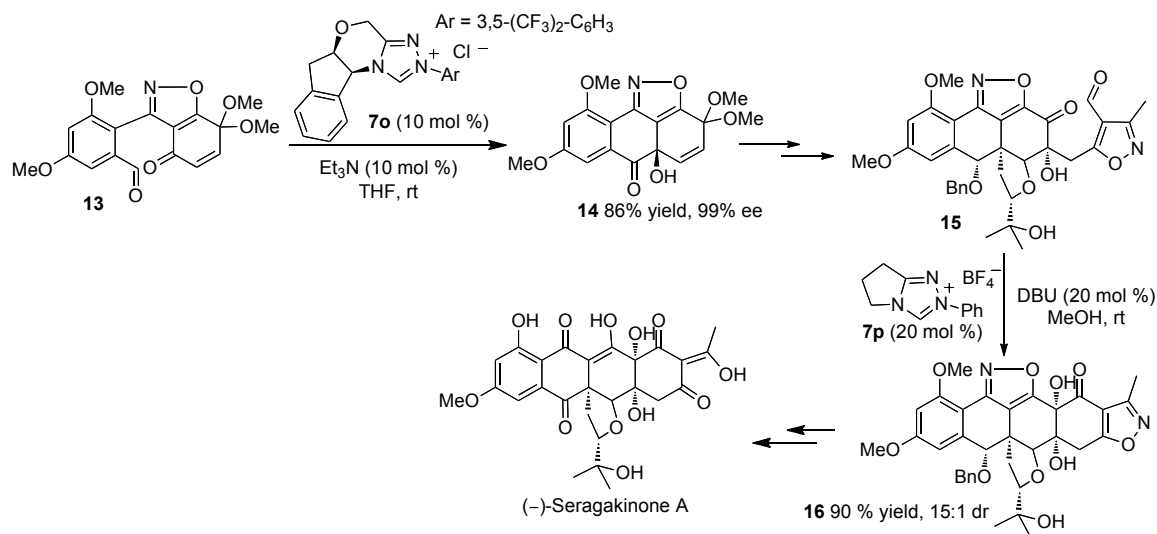
Scheme 1.12 Highly Diastereoselective Intramolecular Aldehyde-Ketone Benzoin Cyclization.²¹

An enantioselective version of the intramolecular benzoin reaction was performed by the Sakai group through the desymmetrization of cyclic 1,3-diketones (Scheme 1.13). A bicyclic tertiary alcohol was obtained in excellent enantioselectivity and diastereoselectivity (up to 90% yield, >99% ee, >99% de).²¹ However, the transformation required the use of a high catalytic loading of chiral triazolium salt **7n**, and furthermore, only the use of α -methyl substituents was reported.



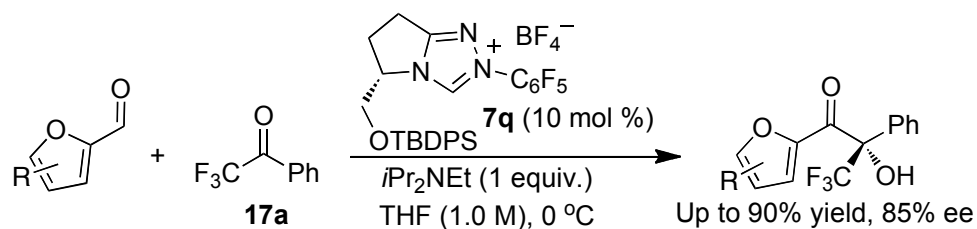
Scheme 1.13 NHC-Catalyzed Desymmetrization of 1,3-Diketones to Access α -Hydroxy Bicyclic Ketones.

The usefulness of the intramolecular cross-benzoin reaction was illustrated in two separate cyclizations for the synthesis of (–)-seragakinone A, an antifungal and antibacterial natural product (Scheme 1.14).²²



Scheme 1.14 Application of the Intramolecular Aldehyde-Ketone Cross-Benzoin Reaction for the Synthesis of (-)-Seragakinone A.

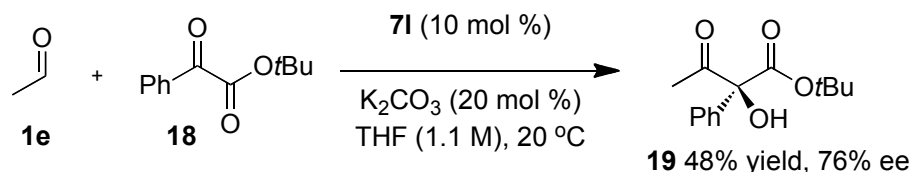
Recently, Enders and coworkers developed an intermolecular variant of the aldehyde-ketone crossed-benzoin reaction using highly activated ketones with heteroaromatic aldehydes in good chemoselectivity.²³ Moderate to good enantioselectivity of the cross-coupling of heteroaromatic aldehydes with aryl trifluoromethyl ketones was obtained with chiral triazolium salt **7q** (up to 85% ee, Scheme 1.15).



Scheme 1.15 Enantioselective Intermolecular Aldehyde-Ketone Cross-Benzoin Reaction.

Alkyl- and aryl-substituted α -ketoesters were also shown to be highly reactive substrates for the aldehyde-ketone cross-benzoin reaction with aliphatic aldehydes catalyzed by achiral, electron-deficient triazolium **7k**.²⁴ Most interestingly, the cross-

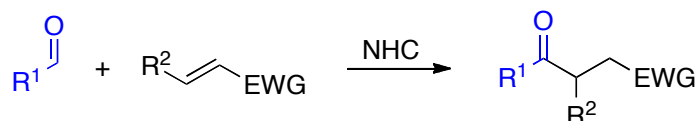
coupling of aliphatic, aryl, and heteroaromatic aldehydes with aryl substituted α -ketoesters was achieved selectively. Despite the wide scope of the reaction, only one enantioselective example was shown, in which the cross-benzoin product is obtained in moderate yield and enantioselectivity at ambient temperature (Scheme 1.16).



Scheme 1.16 Chemo- and Enantioselective Aldehyde-Ketone Cross-Benzoin Reaction of α -Ketoesters with Aliphatic Aldehydes.

1.2 Stetter Reactions

More than three decades after Ukai's first report on the thiamin-mediated benzoin reaction, Stetter and Schreckenbergr introduced the use of electron-poor olefins as electrophiles (Scheme 1.17).²⁵ The 1,4-addition of acyl anion equivalents onto Michael acceptors leads to the formation of a new C-C bond, in addition to the creation of a new stereogenic centre. Through this transformation, 1,4-dicarbonyl compounds can be accessed, a structural feature found in numerous natural products.²⁶ Although the Stetter reaction is plagued with the formation of the benzoin product, as previously mentioned, the benzoin reaction is reversible for most cases.¹⁴ To suppress the formation of benzoin side products, aldehyde surrogates, such as acyl silanes,²⁷ α -diketones,²⁸ and sodium pyruvate²⁹ were employed for the Stetter reaction to generate the acyl anion equivalent required for the transformation.



Scheme 1.17 Stetter Reaction: Addition of an Acyl Anion Equivalent to Electron-Poor Olefins.

In contrast to the intermolecular Stetter reaction, the intramolecular variant has been intensively investigated, in which high yields and enantioselectivities have been achieved.³⁰ In 1996, Enders reported the first asymmetric version of the reaction, achieving moderate yields and moderate enantioselectivity (up to 73% yield, 74% ee).³¹ Thereafter, Rovis and coworkers made significant progress in the intramolecular Stetter reaction through the development of new chiral triazolium salts (Figure 1.4).³² Through steric and electronic modulations of the triazolium salts, improvement in both the yield and enantioselectivity of the reaction was achieved to access 5- and 6-membered rings (Scheme 1.18). The formation of larger rings (>7) proved to be more challenging. Various electron-withdrawing functional groups on the acceptor portion were well tolerated, such as: α,β -unsaturated esters, thioesters, amides, ketones, aldehydes, cyanides, and phosphonates. Furthermore, the scope of the reaction could be extended to the stereoselective generation of all-carbon quaternary stereogenic centres (Scheme 1.19).³³

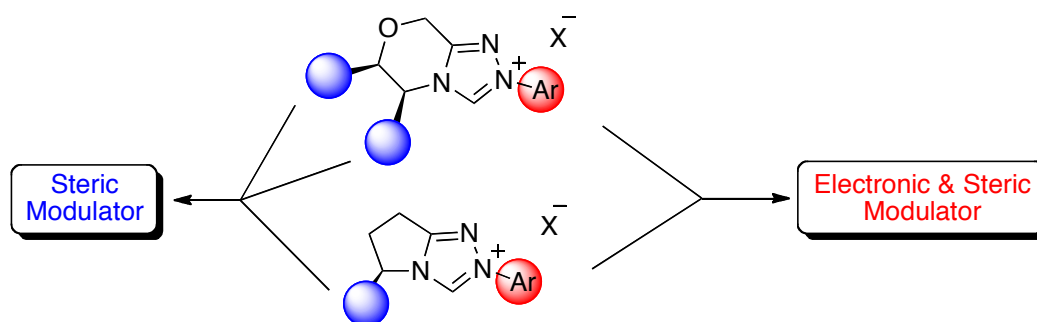
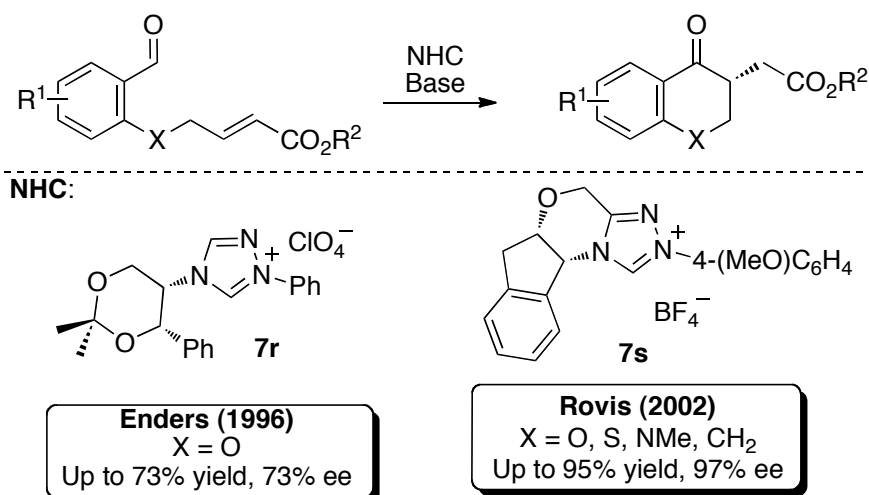
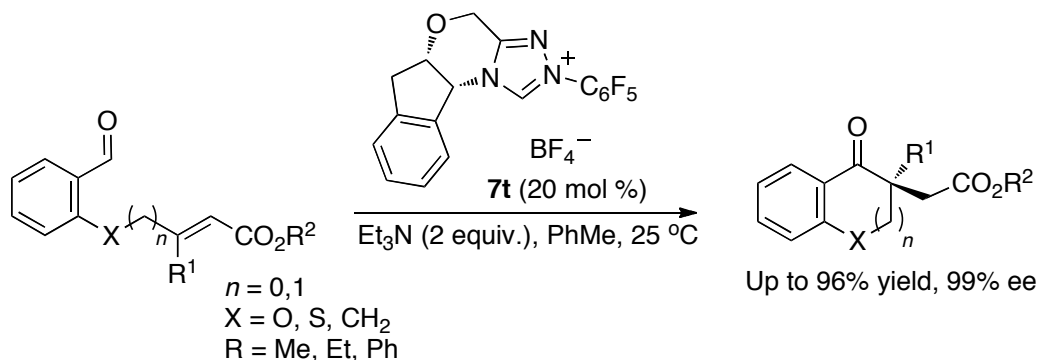


Figure 1.4 NHC Precatalyst Designs through Steric and Electronic Modulation.



Scheme 1.18 NHC Precatalysts for the Stereoselective Intramolecular Stetter Reaction.³¹⁻³²

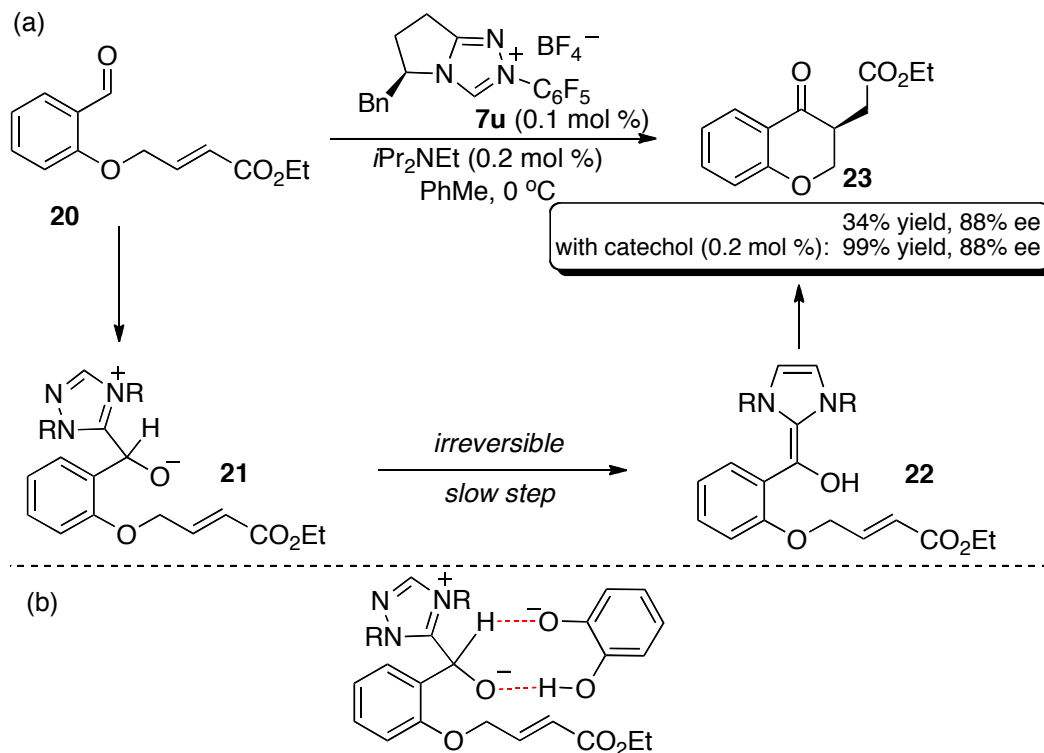


Scheme 1.19 NHC-Catalyzed Intramolecular Stetter Reaction for the Generation of All-Carbon Quaternary Stereogenic Centres.

In 2011, Rovis and coworkers reported a mechanistic study of the intramolecular Stetter reaction of substrate **20** with triazolium salt **7u** (Scheme 1.20a).³⁴ The results determined from the rate law, kinetic isotope effects, and competition experiments suggest that the proton transfer step to form the Breslow intermediate is the first irreversible step and the rate-determining step of the transformation. Catechol was proposed to assist in the proton transfer step of the transformation through hydrogen bonding interactions, thereby facilitating the turnover of the catalyst (Scheme 1.20b).³⁵ Indeed, a significant improvement of the yield of the reaction can be achieved in the

presence of catechol at a record low catalytic loading of 0.1 mol % of the triazolium salt

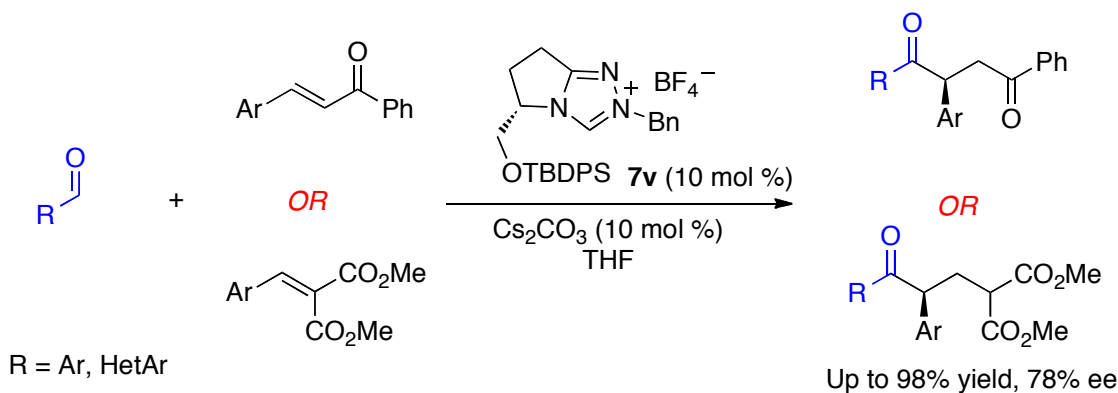
7u.



Scheme 1.20 Mechanistic Investigation of the Intramolecular Stetter Reaction and Proposed Mode of Activation of Catechol.³⁴⁻³⁵

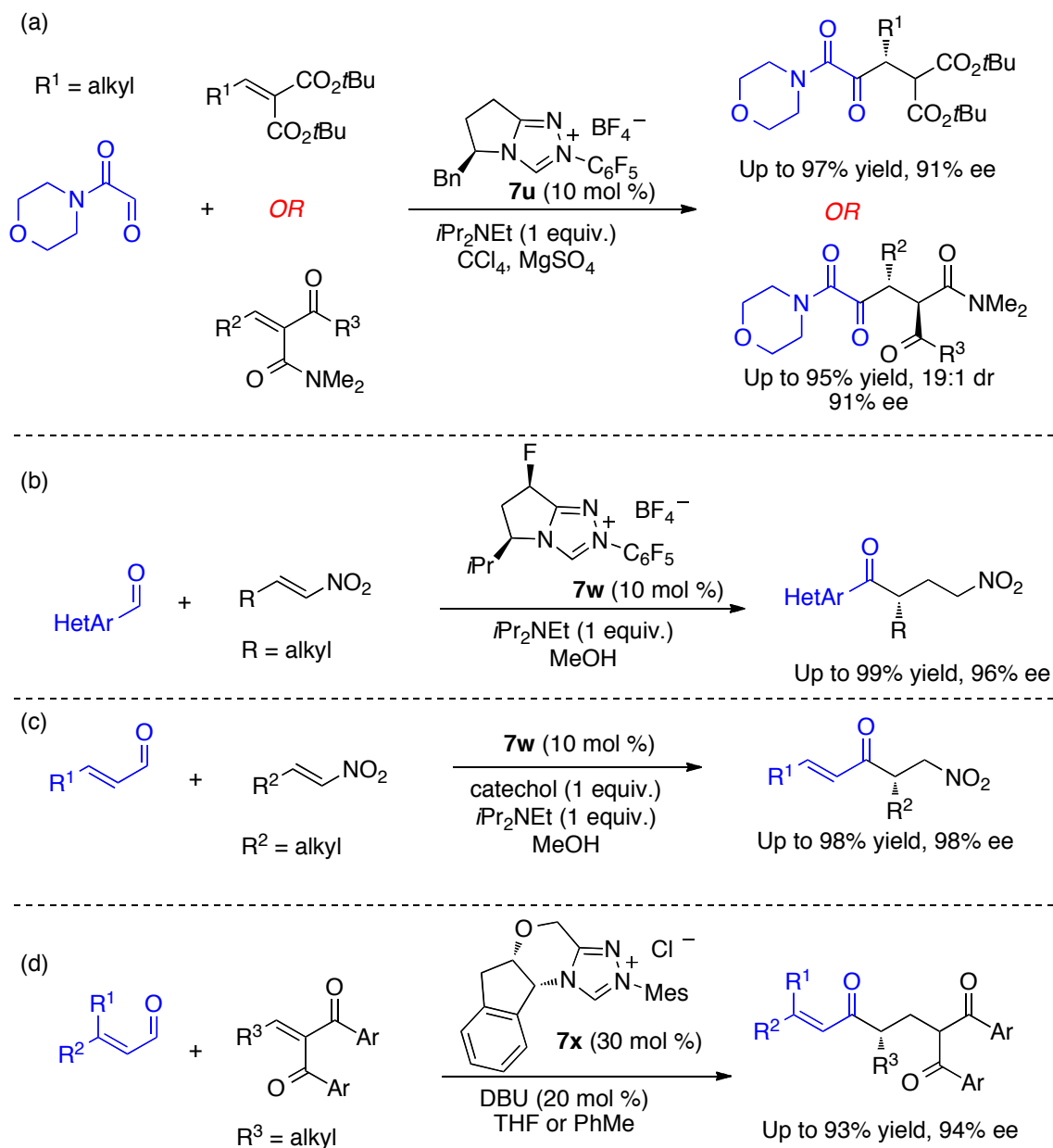
Unlike the intramolecular Stetter reaction, the intermolecular counterpart has received less attention. Soon after Stetter introduced the use of electron-poor olefins for the addition of acyl anion equivalents, Trost and coworkers illustrated in one example, that the Stetter reaction can be performed with a β,β -disubstituted α,β -unsaturated ester, catalyzed by a thiazolium salt, for the synthesis of (\pm)-hirsutic acid C.³⁶ Initial investigation of the asymmetric intermolecular Stetter reaction, by Enders and coworkers with chiral thiazolium salts resulted in low yields and enantioselectivity (4% yield, 39% ee).³⁷ It was not until 2008 that Enders and coworkers reported a significant improvement with chiral triazolium salts in the yield and enantioselectivity of the

intermolecular Stetter reaction between aryl- and heteroaromatic aldehydes with arylidene malonates and chalcone derivatives (up to 98% yield, 78% ee, Scheme 1.21).³⁸



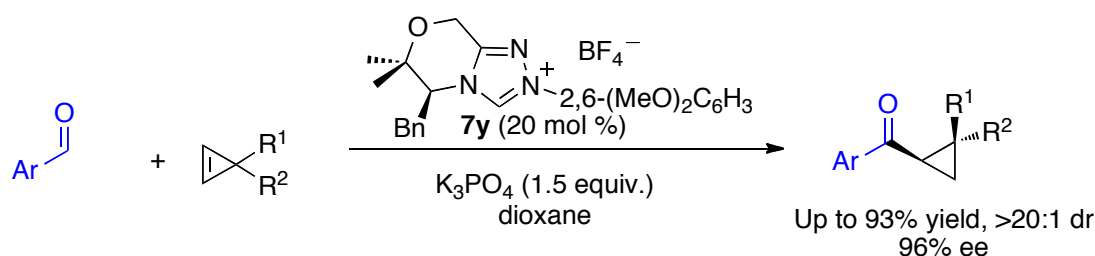
Scheme 1.21 Recent Advances in the Stereoselective Intermolecular Stetter Reaction.

Concurrent to Ender's report, Rovis and coworkers reported a highly enantioselective intermolecular Stetter reaction of highly reactive glyoxamides with alkylidenemalonates³⁹ and alkylidene ketoamides⁴⁰ (up to 91% ee, Scheme 1.22a). Furthermore, the same group expanded the scope of the reaction to achieve excellent enantioselectivity with 2-heteroaromatic aldehydes and β -alkyl nitroalkenes (Scheme 1.22b).⁴¹ The reaction is restricted to secondary alkyl β -substituents to preserve high enantioselectivity as linear alkyl substituents result in a significant decrease in enantiomeric excess (72-74% ee). Most intriguingly, α,β -unsaturated aldehydes, which have been shown to predominantly undergo homoenolate reactivity (*vide infra*), were found to undergo acyl anion equivalent 1,4-addition, in the presence of catechol as an additive, onto alkyl nitro alkenes in high yields and high enantioselectivity (Scheme 1.22c).³⁵ Following Rovis' report, Chi and coworkers found that acyl anion additions of enals onto modified chalcone derivatives can proceed in high yields and high enantiomeric excess without the need for additives (Scheme 1.22d).⁴²



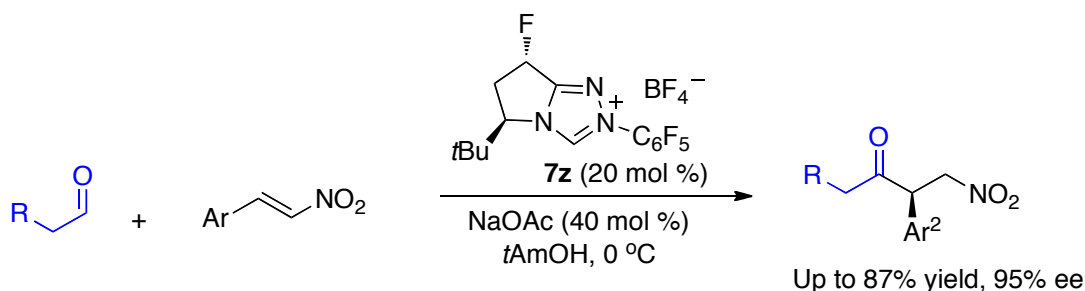
Scheme 1.22 Recent Advances in the Stereoselective Intermolecular Stetter Reaction.³⁹⁻⁴²

Notably, Glorius and coworkers have recently illustrated the use of unactivated, strained cyclopropanes as acceptors for the Stetter reaction with aryl aldehydes (Scheme 1.23).⁴³ Despite these improvements in the intermolecular Stetter reaction, the current methodologies are still restricted to specific substrate combinations.



Scheme 1.23 Recent Advances in the Stereoselective Intermolecular Stetter Reaction with Unactivated, Strained Cyclopropanes.

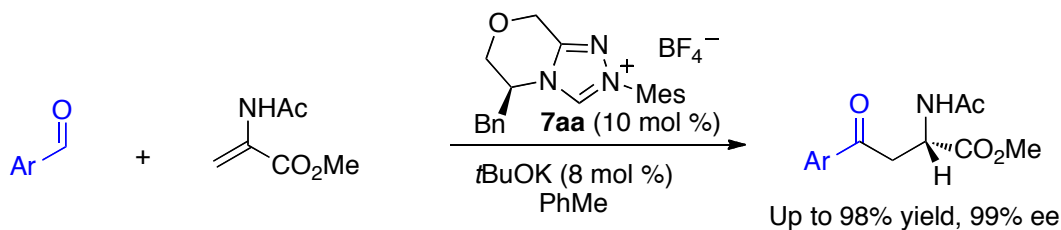
The extension of the Stetter reaction to aliphatic aldehydes is challenging, due to the low relative reactivity of the aldehyde and the presence of enolizable protons under basic conditions. Good reactivity was observed when acetaldehyde was employed with chalcone derivatives, albeit with poor enantioselectivity (up to 85% yield, 76% ee).⁴⁴ However, it was not until very recently that Rovis and coworkers reported a highly enantioselective intermolecular Stetter reaction was achieved with aliphatic aldehydes and β -aryl nitroalkene (Scheme 1.24).⁴⁵ The reaction is restricted to linear alkyl aldehydes to achieve high enantiomeric excess (up to 95% ee).



Scheme 1.24 Recent Advances in the Stereoselective Intermolecular Stetter Reaction with Aliphatic Aldehydes.

Glorius and coworkers have shown that catalytically generated acyl anion equivalents can undergo Stetter reactions onto unsubstituted *N*-acylamido acrylates, followed by a stereoselective α -protonation to furnish α -amino acid derivatives (Scheme

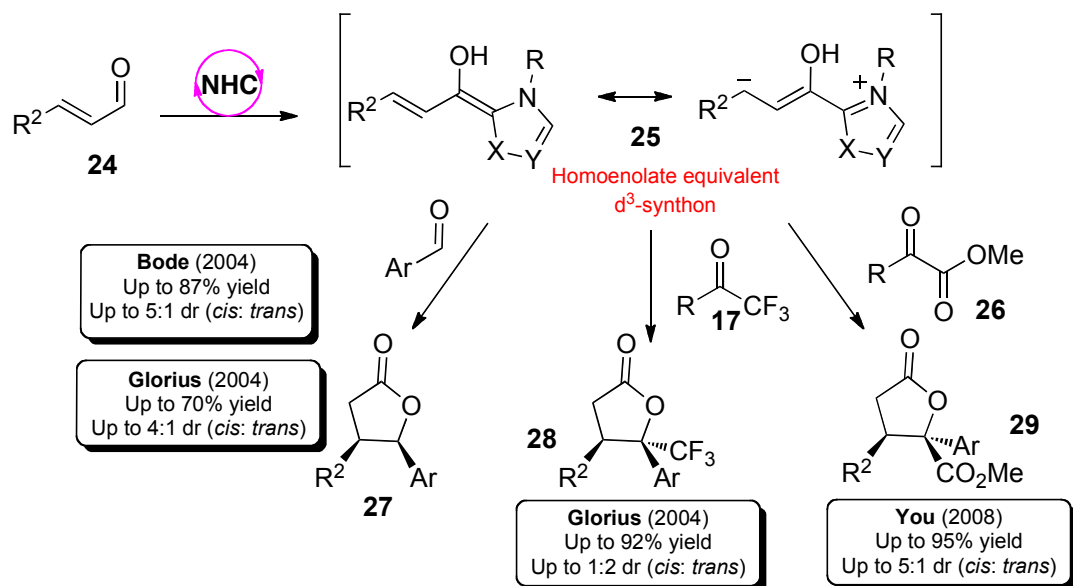
1.25).⁴⁶ Notably, excellent stereinduction can be achieved with chiral triazolium salts, despite the remote position of the chiral catalyst in the transition state.



Scheme 1.25 Recent Advances in the Stereoselective Intermolecular Stetter Reaction to Access α-Amino Ester Derivatives.

1.3 Extended Umpolung Transformations

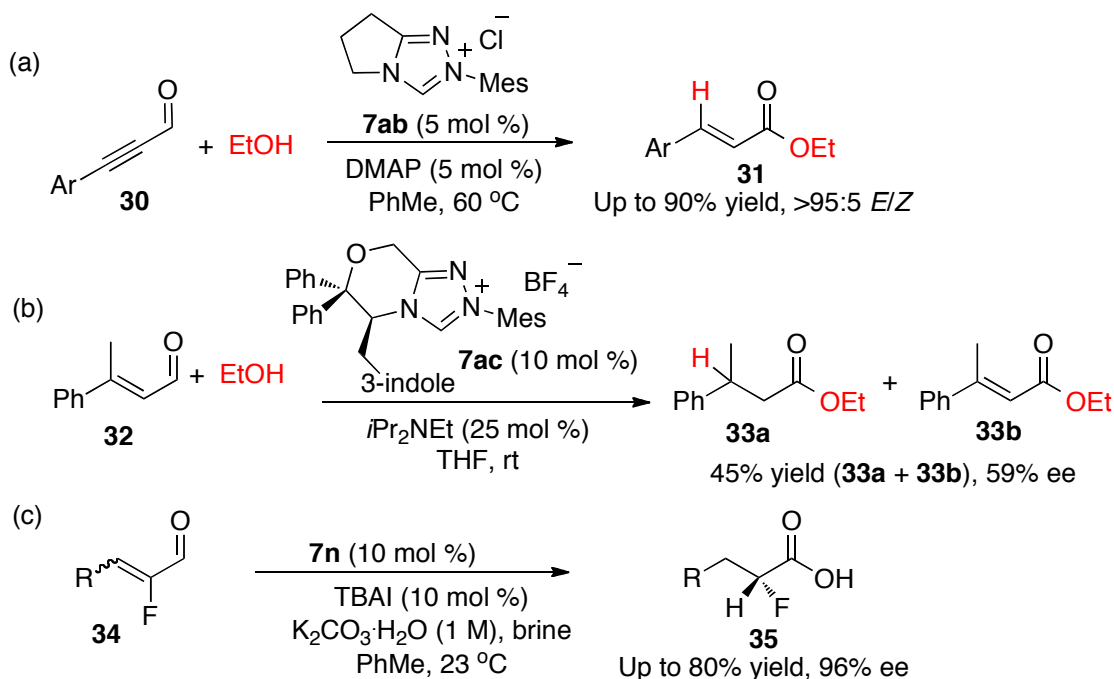
In pioneering studies by Bode et al. and Glorius et al., α,β-unsaturated aldehydes were found to generate homoenolate equivalents in the presence of sterically-hindered imidazolium precatalysts. These d³-synthons are seen to arise from an extended Breslow intermediate **27** (Scheme 1.26).⁴⁷ In the presence of electrophiles, such as aryl aldehydes, highly activated trifluoromethyl ketones **17**,⁴⁷ and α-ketoesters **26**,⁴⁸ the catalytic generation of homoenolate equivalents **25** led to the synthesis of γ-butyrolactones in good yields and good diastereoselectivity.



Scheme 1.26 NHC-Catalyzed Annulations of Enals with Carbonyl Electrophiles to Access Functionalized Lactones.⁴⁷⁻⁴⁸

In addition to carbonyl electrophiles, Scheidt and coworkers have shown that the nucleophilic homoenolate intermediate can react with simple electrophiles, such as a proton to give rise to an enolate intermediate. The susceptibility of the homoenolate intermediate to undergo formal reduction at the β -position led to the development of the internal redox esterification of alkenals and alkynals⁴⁹ (Scheme 1.27a).⁵⁰ Shown by the same group, the enantioselective β -protonation of β,β -disubstituted α,β -unsaturated aldehydes with chiral triazolium salt **7ac** led to modest yield and poor enantioselectivity (58% yield, 55% ee, Scheme 1.27b). Enantioselective protonation at the β -position is difficult to achieve, as the stereocenter formed is far away from the chiral catalyst for efficient stereinduction. On the contrary to the enantioselective protonation at the β -position, α -protonation has been shown by Rovis and coworkers to be achieved in high enantioselectivity. Enantiomerically-enriched α -fluorinated carboxylic acids can be

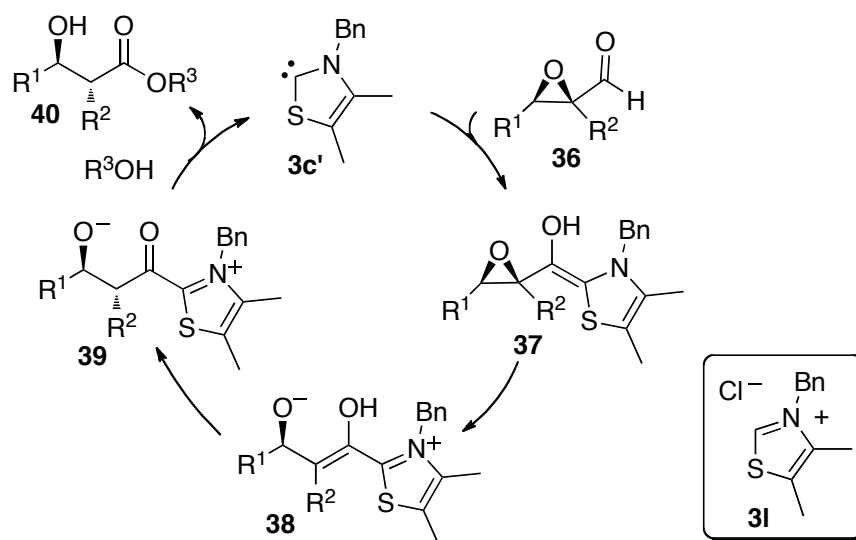
achieved through the internal redox oxidation of β -substituted α -fluoro- α,β -unsaturated aldehydes (up to 96% ee, Scheme 1.27c).⁵¹



Scheme 1.27 NHC-Catalyzed Internal Redox Esterification of Alkenals and Alkynals.⁴⁹⁻⁵¹

Concurrent to the studies on the utilization of the extended umpolung to generate homoenolate and enolate equivalents,⁵² Bode and Rovis have shown that α -reducible aldehydes could be used to perform ring opening of strained cyclic systems⁵³ and α -eliminations.⁵⁴ Ring opening followed by esterification of epoxyaldehydes and *N*-tosyl aziridines could be achieved with thiazolium precatalyst **31** in excellent diastereoselectivity (up to 13:1 dr, *anti:syn*).^{53a} This NHC-catalyzed reaction is a novel alternative method to access carboxylic acid derivatives. As illustrated in Scheme 1.28, the epoxyaldehyde forms a “Breslow intermediate” **37** with the carbene, followed by a ring opening to form alkoxide intermediate **38**. The acyl azolium intermediate **39** is then formed as a result of tautomerization. The stereochemical outcome at the β -carbon is

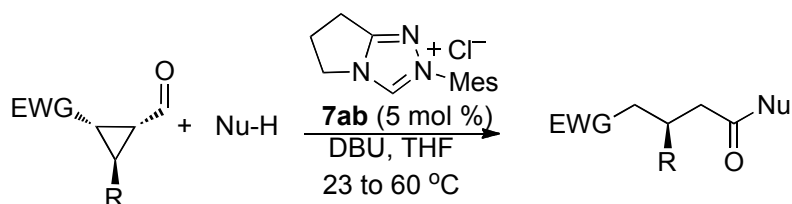
determined in this tautomerization step, with the anti relative configuration being favoured. The nucleophilic addition of an alcohol regenerates the carbene catalyst to provide the β -hydroxyester **40**. Enantiomerically pure epoxyaldehydes are required to obtain enantiomerically enriched products in this reaction. The usefulness of this methodology to access β -hydroxy esters through the NHC-catalyzed internal redox transformation was demonstrated by various groups as part of the synthesis of the natural products, such as (+)-davanone,⁵⁵ largazole, 2-*epi*-largazole,⁵⁶ and a fragment of rhizopodin.⁵⁷



Scheme 1.28 Proposed Mechanism for the NHC-Catalyzed Ring Opening Reaction of Epoxyaldehydes.

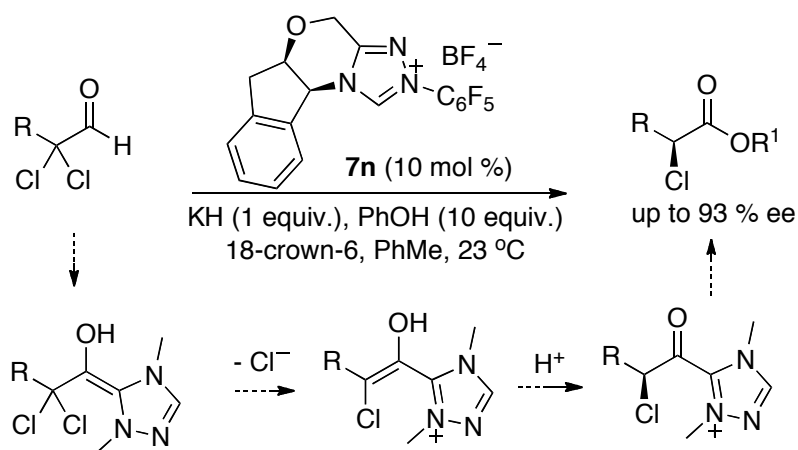
The ring opening of aldehydes was extended to strained chiral formylcyclopropanes, to access chiral β -substituted esters (Scheme 1.29).^{53b} Methyl esters, thiol esters, and carboxylic acids could be accessed directly from strained cyclopropane rings, through the NHC-catalyzed formal internal redox transformation with triazolium precatalyst **7ab**.⁵³ The formylcyclopropanes require activating electron-withdrawing groups, such as ketones, esters, amides, and nitro substituents. Substrates

bearing β -aryl substituent were unreactive. The use of primary and secondary amines as nucleophiles for the transformation can lead to the formation of *N*-alkyl amides.^{53c} However, imidazole as an additive is required to prevent the formation of imines, which were found to hinder the reaction.



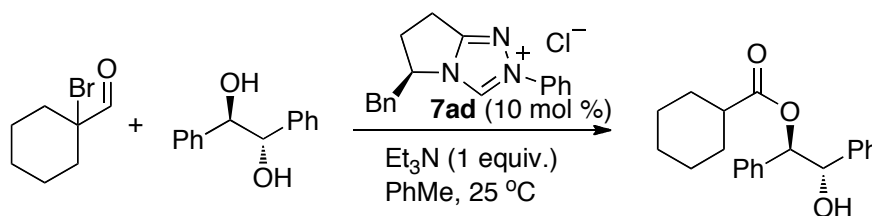
Scheme 1.29 *N*-Mes Triazolium-Derived Carbene Catalyzed Ring Opening of Formylcyclopropanes.

Rovis and coworkers have found that treatment of α,α -dichlorinated aldehydes with chiral triazolium-derived carbenes in the presence of an external nucleophile, such as phenol led to the synthesis of enantiomerically enriched α -chloroesters (Scheme 1.30).⁵⁸ The enantioselectivity of this α -elimination reaction is determined in the protonation step during the formation of the acyl azolium intermediate. Subsequent esterification affords the α -chloroesters in high enantiomeric excess.



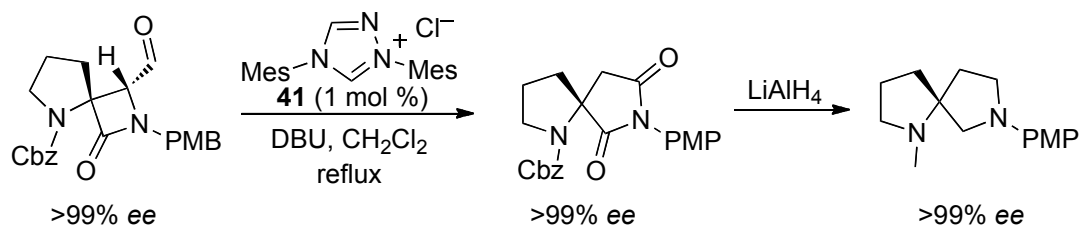
Scheme 1.30 Diastereoselective Protonation of Catalytically Generated Chiral Enolates.

The amidation of aldehydes through ring opening and α -elimination was reported by the same group through relay catalysis with achiral, electron-deficient triazolium salt **7k** and a coupling reagent, such as 1-hydroxy-7-azabenzotriazole (HOAt).^{54c} Selective α -elimination of bromine can be performed with a racemic mixture of α -bromo α -fluoro aldehyde substrates to obtain the α -fluoroester product in high enantioselectivity.^{54c} Furthermore, Rovis and coworkers have shown the use of a chiral carbene and α -bromocyclohexanecarboxaldehyde can promote the desymmetrization of a meso diol in moderate yield and good enantioselectivity (Scheme 1.31).^{54a} However α -eliminations to give access to enantiomerically enriched compounds bearing α -aryl or α -alkyl substituents through stereoselective protonation has yet to be explored.



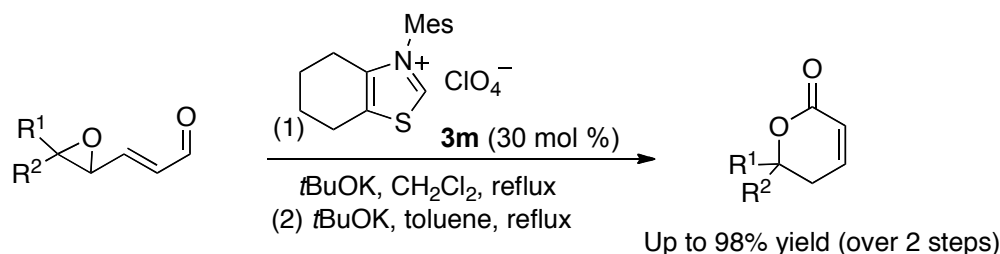
Scheme 1.31 NHC-Catalyzed Desymmetrization of Meso Diols through α -Elimination.

Following the pioneering work of Bode and Rovis on the ring opening and esterification reactions, an intramolecular variation of the reaction was employed in ring expansions by You and coworkers.⁵⁹ Their *N*-Mes imidazolium catalyzed ring expansion of β -lactams to access succinimide derivatives was reported in 2007.^{59a} Enantiomerically-pure, ring-expanded spiro bicyclic diamine could be accessed from enantiomerically enriched starting material (Scheme 1.32).



Scheme 1.32 NHC-Catalyzed Ring Expansion of 4-Formyl-β-Lactams to Access Ring-Expanded Spiro Bicyclic Diamine.

Additionally, She and coworkers further extended Bode's work on the ring opening of epoxyaldehydes to the ring expansion of γ-epoxy-α,β-unsaturated aldehydes to dihydropyrone derivatives in good to excellent yields (Scheme 1.33).⁶⁰



Scheme 1.33 NHC-Catalyzed Ring-Opening of γ-Epoxy-α,β-unsaturated Aldehydes.

1.4 Conclusion

In the last few decades, NHC catalysis has been an area of intensive research.⁶¹ The catalytic addition of 'acyl anion equivalents' has led to the formation of 1,2- and 1,4-difunctionalized compounds in high enantiomeric excess, serving as a useful synthetic tool for C-C bond formations. Furthermore, NHC-generated homoenolate equivalents were found to undergo extended umpolung reactions, giving rise to the development of new reactions. The internal redox transformation of α-reducible functionalizable aldehydes is a synthetically useful tool for the synthesis of various unique structural features, such as β-hydroxyl esters, α-chloro esters, and succinimide derivatives.

However, despite the recent advances in NHC catalysis, the usefulness of these methodologies is severely limited by scope of each reaction. A major limitation of the cross-benzoin reaction is the restriction on specific substrate combinations to achieve high chemoselectivity. Moreover there have been no reports on the highly enantioselective intermolecular cross-benzoin reaction to date.

The intramolecular Stetter reaction has also been intensively investigated. However, the intermolecular counterpart is restricted to highly reactive acceptors and unsubstituted olefins. In recent years, the development of new chiral triazolium salts resulted in significant improvement in the reactivity and stereoselectivity of the intermolecular Stetter reaction. However, highly enantioselective reactions with β -substituted α,β -unsaturated acceptors are typically restricted to 2-heteroaromatic aldehydes, whereas aryl aldehydes are restricted to terminal olefins to achieve excellent enantioselectivity.

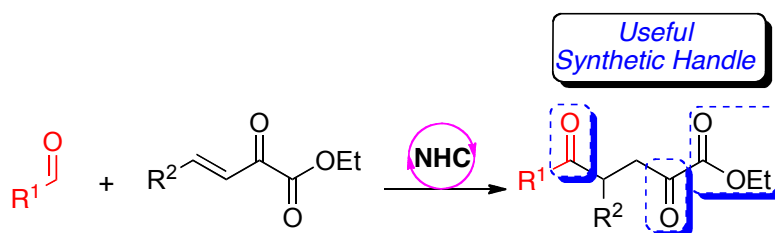
PART II: RESULTS AND DISCUSSION

CHAPTER 2: NHC-CATALYZED INTERMOLECULAR STETTER REACTION

The Stetter reaction, which consists of the NHC-catalyzed addition of an acyl anion equivalent onto Michael acceptors, was first reported in 1973. The intramolecular Stetter reaction was intensively investigated by Ciganek,⁶² Enders, Rovis and many others, high yields and high enantioselectivities of the Stetter adducts were achieved.³¹⁻³⁵ In contrast to the intramolecular Stetter reaction, the intermolecular counterpart has been less explored. Although Enders, Glorius, and Rovis achieved high yields and moderate to high enantioselectivities in recent years, a major limitation to the intermolecular Stetter reaction is the restricted substrate scope.

2.1 Research Objective

To address the limitations of the Stetter reaction, we were interested in introducing β -substituted β,γ -unsaturated- α -ketoesters as acceptors for the intermolecular Stetter reaction. The α -ketoester moiety could serve as a useful synthetic handle, in addition to acting as an activating group (Scheme 2.1). At the time of the study, the use of β -aryl substituted acceptors in the literature only resulted in moderate enantioselectivity for the intermolecular Stetter reaction.³⁸ In contrast, highly enantioselective Stetter reactions were reported with β -alkyl substituted acceptors.⁴⁵ In order to validate the usefulness of α -ketoester acceptors for the intermolecular Stetter reaction, γ -aryl substituted acceptors were explored.



Scheme 2.1 α-Ketoester Moiety as an Activating Group and a Synthetic Handle.

From our group's experience, 2-heteroaromatic aldehydes, such as furfural, are known to be highly reactive aldehydes for the benzoin and Stetter reactions. In contrast to 2-heteroaromatic aldehydes, the use of aryl aldehydes with β-substituted acceptors for the Stetter reaction typically resulted in poor conversion and moderate enantioselectivity.^{102a} The difference in reactivity between the two classes of aldehydes was proposed to be a consequence of the steric interactions of the Breslow intermediate and the β-substituent of the acceptor.³⁵ The ortho C-H group on the catalyst's aromatic moiety significantly hinders the approach of the Breslow intermediate towards the Stetter addition (Figure 2.1). In contrast, the Breslow intermediate formed with 2-heteroaromatic aldehydes, avoid such an unfavourable interaction. Therefore, furfural was initially chosen as the model aldehyde in order to investigate the potential of the α-ketoester acceptors for the intermolecular Stetter reaction.

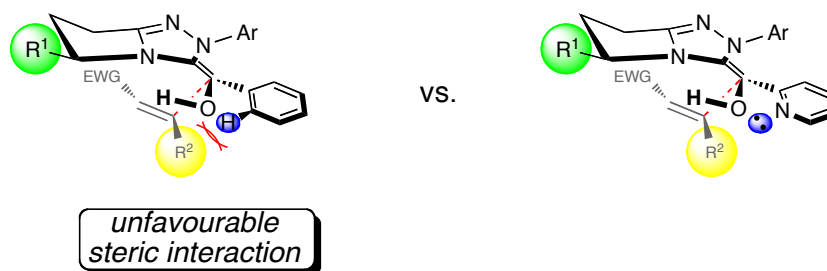
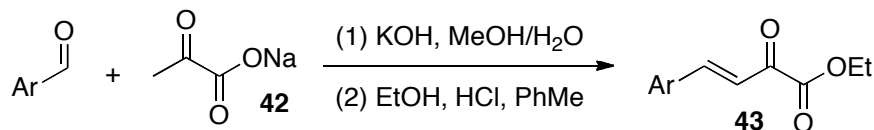


Figure 2.1 Rationale for the Poor Reactivity Observed with Aryl Aldehydes for the Stetter Reaction with β-Substituted Acceptors.

γ -Aryl- β,γ -unsaturated- α -ketoesters **43** were synthesized in one-pot from the appropriate aldehyde and sodium pyruvate through an aldol condensation, followed by a Fischer esterification (Scheme 2.2).



Scheme 2.2 General Synthetic Route to Access γ -Aryl- β,γ -Unsaturated- α -Ketoesters Acceptors.

2.2 α -Ketoester As Useful Acceptors for the Intermolecular Stetter Reaction

2.2.1 Optimization of the Reaction

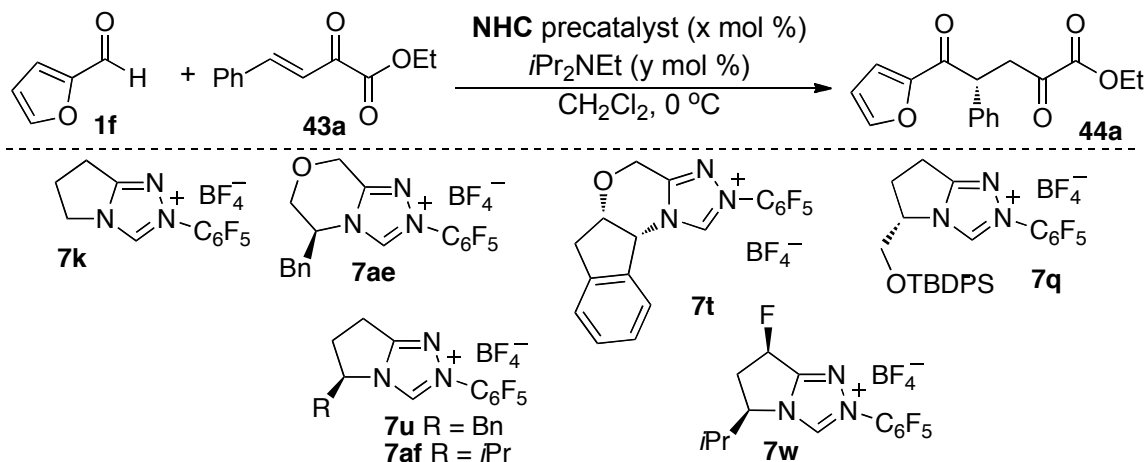
Eduardo Sánchez-Larios performed all of the optimization experiments with β -aryl acceptor **46a** and heteroaromatic aldehyde **1f**.⁶³ Through a base and solvent screening, *i*Pr₂NEt and dichloromethane were found to be the optimal baseⁱ and solventⁱⁱ for the Stetter transformation of model acceptor **43a** and heteroaromatic aldehyde **1f** with achiral triazolium salt **7k**. A catalyst screening revealed fluorinated triazolium salt **7w** to be the superior catalyst for the transformation (Table 2.1, entry 7). Experiments performed with morpholinone-derived carbene salt **7ae** resulted in no reaction, and the use of Rovis' catalyst **7t** resulted in low conversions. Reactions performed with triazolium salts **7q**, **7u**, and **7af** resulted in good conversions and moderate to good enantioselectivity (entries 4-6). When fluorinated triazolium salt **7w** was employed, a

ⁱ In addition to *i*Pr₂NEt, bases such as DBU and cesium carbonate were also investigated by Eduardo Sánchez-Larios.

ⁱⁱ Solvents such as THF, toluene, and ethanol were also investigated.

significant improvement in the enantioselectivity of the reaction and good yields were obtained.

Table 2-1 Stetter Reaction: Optimization of the Reaction Conditions with Model Acceptor **46a** and Furfural **1f**.^a



entry	NHC precatalyst (x mol %)	<i>i</i> Pr ₂ NEt (y mol %)	time (min)	yield (%) ^b	ee (%) ^c
1	7k (30)	30	120	95	-
2	7ae (30)	30	(7 h)	0	-
3	7t (30)	30	30	20	28
4	7q (30)	30	300	69	76 ^d
5	7u (30)	30	300	88	80
6	7af (30)	30	30	96	80
7	7w (30)	30	120	90	86
8	7w (10)	100	15	98	89
9	7w (5)	100	15	92	90
10	7w (1)	100	240	20	82

^a Unless otherwise noted, all reactions were performed by the addition of *i*Pr₂NEt (1 equiv.) to a solution of acceptor **43a** (1 equiv.), aldehyde (1.5 equiv.), and precatalyst in dichloromethane (0.2 M) at 0 °C. ^b Isolated yield. ^c Enantiomeric excess was determined using HPLC on chiral stationary phase. ^d The opposite enantiomer was obtained.

At 10 mol % catalytic loading of **7w**, the reaction time was reduced to 15 min when a stoichiometric amount of base was used, with no significant erosion of the enantiomeric excess of the Stetter product observed (entry 8). Gratifyingly, lowering the

catalytic loading from 10 to 5 mol % resulted in comparable yields and enantioselectivity (entry 9). However, further decreasing the catalyst loading to 1 mol % resulted in a significant decrease in the yield and enantioselectivity of the reaction (entry 10). With the optimal conditions on hand (entry 9), resulting in the highest enantioselectivity of 90% ee, the scope of the reaction was then investigated.

2.2.2 Scope of the Reaction

Following the optimization of the reaction conditions, the scope of the reaction was explored with various heteroaromatic aldehydes and model α -ketoester acceptor **46a**. Although good yield and good enantioselectivity was observed with furfural **1f** (Table 2-2, entry 1), rapid erosion of the enantiomeric excess of the Stetter product (0% ee, not shown) was observed when the reaction was performed at a larger scale (2.30 mmol vs. 0.10 mmol).ⁱⁱⁱ As a result of this erosion, the procedure was then modified, the base was added as a solution in dichloromethane and the product was obtained in 88% yield, 89% ee (entry 2). The use of 5-methyl furfural **1g** resulted in a comparable yield at longer reaction times (entry 3). The prolonged reaction time required for complete conversion was presumably a result of electronic effects, as the methyl substituent was acting as an electron-donating group. In addition to the longer reaction time required, Stetter product **44b** was obtained in a lower enantiomeric excess (84% ee). Benzo[*b*]furan-2-carboxaldehyde **1h** resulted in rapid conversion to the desired Stetter product (entry 4). However, the product could not be isolated in pure form. The enantioselectivity of the reaction with **1h** was found to be much lower than with aldehydes **1f** and **1g**. The position of the heteroatom relative to the aldehyde was apparently crucial for its

reactivity, as the use of 3-furaldehyde **1i** resulted in long reaction times and racemic products (entry 5). Sulfur-containing heterocycle **1j** was unreactive under the reaction conditions even with high catalyst loading and no reaction was observed at ambient temperatures (entry 6).

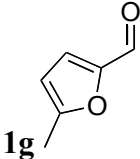
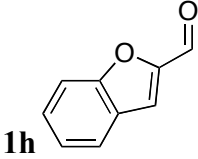
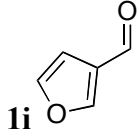
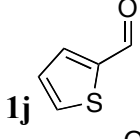
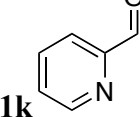
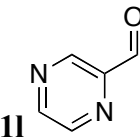
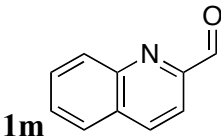
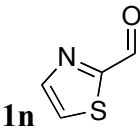
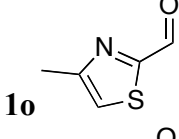
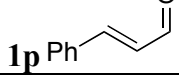
Gratifyingly, nitrogen-containing heterocycles can be used in the reaction. The use of 2-pyridyl carboxaldehyde **1k** resulted in good yield and good enantioselectivity (entry 7). Pyrazine 2-carboxaldehyde **1l** resulted in comparable result (entry 8), whereas the Stetter product was obtained in excellent enantioselectivity when using quinoline-2-carboxaldehyde **1m** (entry 9).

Using thiazole heterocyclic carboxaldehydes **1n** and **1o** afforded in moderate yields and moderate enantioselectivity (entries 10-11). Unsaturated aldehydes such as cinnamaldehyde **1p** were found to be unreactive in this transformation (entry 12). The reaction with γ -aryl α -ketoester acceptors appears to be restricted to a narrow scope of 2-heterocyclic carboxaldehydes, a common limitation observed with the existing methodologies for the intermolecular Stetter reaction.

Table 2-2 Stetter Reaction: Scope of the Reaction with Model α -Ketoester **43a**.^a

entry	aldehyde	time (min)	product	yield (%) ^b	ee (%) ^c
1 2 ^e		15 30	44a	92 ^d 88	90 ^d 89

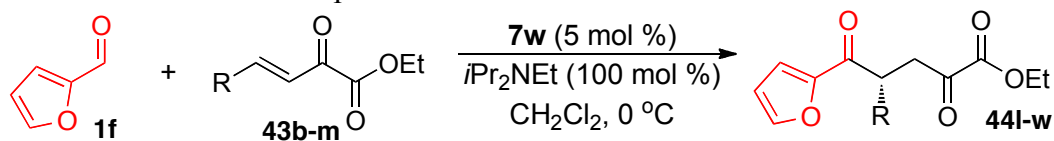
ⁱⁱⁱ Observation was made by Eduardo Sánchez-Larios

3 ^f		(4.5 h)	44b	89	84
4		10	44c	(>95% conv.)	73
5 ^{g,h}		(48 h)	44d	31	0
6 ^{f,g}		(72 h)	44e	0	-
7 ^d		10	44f	88	91
8 ^d		15	44g	94	87
9 ^d		30	44h	95	>99
10		40	44i	44	76
11		90	44j	73	75
12 ^{g,i}		(48h)	44k	0	-

^a Unless otherwise noted, all reactions were performed by the addition of base to a solution of acceptor **43a** (1 equiv.), aldehyde (1.5 equiv.), and precatalyst **7w** (0.05 equiv.) in dichloromethane (0.2 M) at 0 °C. ^b Isolated yield. Conversion determined by ¹H NMR of the crude reaction mixture is given in parenthesis. ^c Enantiomeric excess was determined using HPLC on chiral stationary phase. ^d Reactions were performed by Eduardo Sánchez-Larios. ^e Reaction was performed at 2.3 mmol scale. ^f Reaction was performed with 10 mol % catalytic loading. ^g Reaction was performed at 23 °C. ^h Reaction was performed with 20 mol % catalytic loading at 23 °C. ⁱ Reaction was performed with 30 mol % catalytic loading.

Various γ -substituted α -ketoester acceptors were investigated with furfural **1f**. Fluorinated and brominated acceptors **43b** and **43c** resulted in rapid conversion to the Stetter product in 90% ee (Table 2-3, entries 1-2). However, the use of electron-donating substituents significantly reduced the reactivity of the acceptor. Indeed, 4-methoxyphenyl **43d** reacted sluggishly, resulting in moderate yield and no enantioselectivity (entry 3). In contrast, the more electrophilic 3-methoxy phenyl acceptor **46e** furnished the Stetter product in excellent yield and high enantioselectivity (entry 4). The use of 3,4-dimethoxyphenyl acceptor **43f** resulted in rapid conversion to the Stetter adduct, but the reaction was only moderately enantioselective (77% ee, not shown). Gratifyingly, increasing the catalytic loading to 10 mol % improved the enantiomeric excess to 90% (entry 5). The use of 2-naphthyl substrate **43g** led to the formation of the Stetter adduct in excellent yield and high enantioselectivity (entry 6). However, heteroaryl acceptors **43h-i** resulted in poor reactivity, low to good yields and racemic products (entries 7-8). On the other hand, the use of 3-furfuryl substrate **43j** led to the Stetter product in moderate yields and good enantioselectivity (entry 9). Rapid conversion to the Stetter product was observed with the less electron-rich acceptor **43k**. The Stetter adduct was obtained in moderate enantiomeric excess (entry 10). However, the product could not be isolated in pure form. Acceptor **43l** was found to be unreactive in this transformation (entry 11). Unfortunately, the reaction was not applicable to γ -alkyl α -ketoester **43m**, presumably due to the poor reactivity of the acceptor, resulting in low conversion (entry 12).

Table 2-3 Stetter Reaction: Scope of the Reaction with Furfural **1f** and Various β -Substituted α -Ketoester Acceptors.^a



entry	acceptor (R)	time (min)	product	yield (%) ^b	ee (%) ^c
1 ^d	43b 4-FC ₆ H ₄ -	<5	44l	80	90
2 ^d	43c 4-BrC ₆ H ₄ -	<5	44m	90	90
3 ^d	43d 4-MeOC ₆ H ₄ -	(62h)	44n	62	0
4 ^d	43e 3-MeOC ₆ H ₄ -	10	44o	96	90
5 ^e	43f 3,4-(MeO) ₂ C ₆ H ₃ -	75	44p	86	90
6	43g 2-naph-	10	44q	97	90
7	43h 2-thiophenyl-	(24h)	44r	80	0
8 ^f	43i 2-furfuryl-	(24h)	44s	34	0
9	43j 3-furfuryl-	(2h)	44t	63	88
10	43k 3-pyridyl	5	44u	(>99% conv.)	77
11	43l <i>trans</i> -PhCH=CH-	(24h)	44v	0	-
12 ^d	43m hexyl	(24h)	44w	(10% conv.)	-

^a Unless otherwise noted, all reactions were performed by the addition of base to a solution of acceptor **43** (1 equiv.), aldehyde **1f** (1.5 equiv.), and precatalyst **7w** (0.05 equiv.) in dichloromethane (0.2 M) at 0 °C. ^b Isolated yield. Conversion determined by ¹H NMR of the crude reaction mixture is given in parenthesis. ^c Enantiomeric excess was determined using HPLC on chiral stationary phase. ^d Reactions were performed by Eduardo Sánchez-Larios. ^e Reaction was performed with 10 mol % cat. loading. ^f Reaction was performed with 10 mol % cat. loading at 23 °C.

Although no obvious trend could be observed with the scope of the reaction, reactions resulting in low reactivity and consequently requiring long reaction times (>1h, Table 2-3, entries 3, 7-8) resulted in poor enantioselectivity. The poor enantioselectivity of the reaction could be a consequence of the susceptibility of the Stetter products to undergo racemization during the extended reaction times.

The absolute configuration of the Stetter adducts obtained with triazolium salt **7w** were tentatively assigned by analogy to Rovis' intermolecular Stetter reaction with alkyl nitro alkenes and 2-heteroaromatic aldehydes.^{iv,102a}

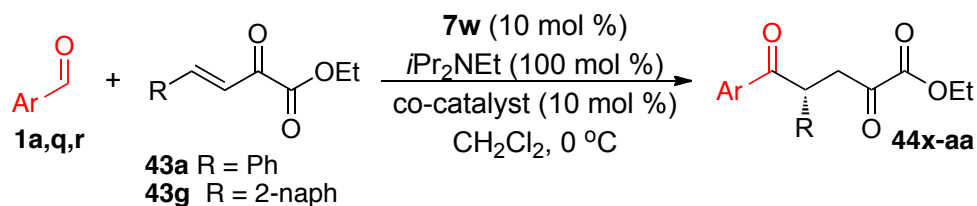
Extension of the Stetter reaction to aryl aldehydes with the α -ketoester acceptors was explored. Gratifyingly, the reaction with phenyl and electron-poor phenyl aldehydes **1a,q,r** furnished the desired Stetter product, albeit in low yields, and moderate enantioselectivity (Table 2-4, entries 1-3). Despite the low yield, the transformation was a promising result, as aryl aldehydes were previously found to be unreactive with β -alkyl nitroalkene acceptors in the Stetter reaction.⁴¹ The promising result observed with aryl aldehydes led to the preliminary study of the intermolecular Stetter reaction with γ -aryl α -ketoester acceptors. 2-Naphthyl acceptor **46g** was employed as the model acceptor, due to the ease of its preparation. Under the optimized conditions for 2-heteroaryl aldehydes and γ -aryl α -ketoester acceptor, benzaldehyde was explored with model acceptor **46g**. Unfortunately, low yields and moderate enantioselectivity were observed (entry 4). Following extensive optimization of the reaction through a catalyst, solvent, base, and concentration study, no improvement in the yield or the enantioselectivity was observed.

Based on the success observed with Lewis acids as co-catalysts for NHC-catalyzed homoenolate reactions by Scheidt and coworkers,⁶⁴ Ti(OiPr)₄ and Mg(OtBu)₂ were explored as co-catalysts. The use of Ti(OiPr)₄ as Lewis acid resulted in no Stetter reaction and slow decomposition of the acceptor (entry 5). Furthermore, the rapid

^{iv} Efforts by Eduardo Sánchez-Larios to determine the absolute configuration of **44m** through crystallization and derivatization for x-ray crystallography were not fruitful.

formation of the benzoin product, typically observed for the intermolecular Stetter reaction, did not occur in this case. In contrast, the use of magnesium as co-catalyst improved the enantioselectivity of the reaction from 65 to 91% ee, but did not lead to an increase in the yield (entry 6). The reason for the improvement in the enantioselectivity of the reaction is not clear at this point. Modifying the source of magnesium to $\text{MgBr}_2\text{Et}_2\text{O}$ resulted in reduced reactivity and reduced enantioselectivity (entry 7). Unfortunately, despite the various efforts to improve the conversion, the best isolated yield of the Stetter adduct was 24% (entry 6). Rapid conversion to the Stetter product was observed in the first 30 minutes. However, no significant improvement in the conversion was observed after prolonged reaction time. Presumably, the carbene species was no longer active after extended reaction times, resulting in the low conversion. At this stage, the reason behind the rapid termination in reactivity of the carbene catalyst is unknown. Notably, the order of addition of the reagents was critical for the reactivity of the carbene catalyst. Generation of the carbene catalyst in the presence of the α -ketoester acceptor prior to the addition of aldehyde was found to completely shut down the reaction. The reaction did not furnish the desired Stetter adduct, nor was any benzoin product observed after 24 h. This observation led to the conclusion that the carbene catalyst may have undergone an irreversible addition onto the α -ketoester acceptor, therefore preventing the benzoin and Stetter transformations.

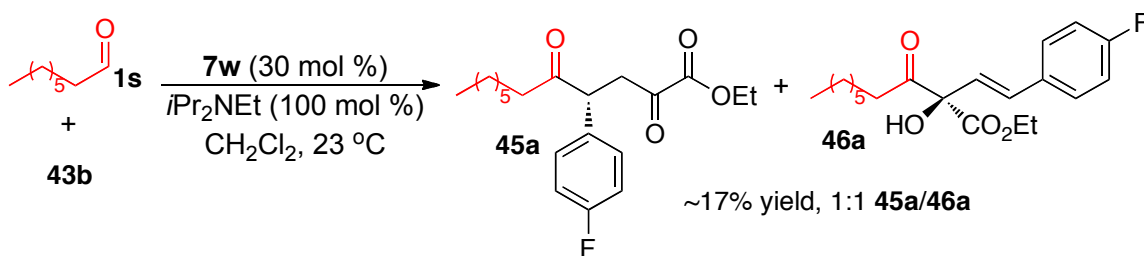
Table 2-4 Stetter Reaction: Scope of the Reaction with Aryl Aldehydes and α -Ketoester Acceptor.^a



entry	Ar	acceptor	co-catalyst	time (h)	product	yield (%) ^b	ee (%) ^c
1 ^d	1a Ph-	43a	none	4	44x	18	57
2 ^d	1q 4-(CF ₃)C ₆ H ₄	43a	none	3	44y	(13)	nd
3 ^d	1r 4-(MeO ₂ C)C ₆ H ₄	43a	none	3	44z	30	68
4	1a	43g	none	24	44aa	37	65
5	1a	43g	Ti(OiPr) ₄	24	44aa	0	-
6	1a	43g	Mg(OtBu) ₂	24	44aa	24	91
7	1a	43g	MgBr ₂ ·Et ₂ O	24	44aa	(11)	55

^a Unless otherwise noted, all reactions were performed by the addition of *i*Pr₂NEt (1 equiv.) to a solution of acceptor (1 equiv.), aldehyde (1.5 equiv.), and precatalyst **7w** (0.1 equiv.) in dichloromethane (0.2 M) at 0 °C. ^b Isolated yield. Conversion determined by ¹H NMR of the crude reaction mixture is given in parenthesis. ^c Enantiomeric excess was determined using HPLC on chiral stationary phase. ^d Reactions were performed by Eduardo Sánchez-Larios.

Discouraged by the lack of improvement in the conversion of the Stetter reaction with aryl aldehydes, aliphatic aldehydes were then investigated with γ -aryl α -ketoester acceptors. Octanal **1s** was employed for the intermolecular Stetter reaction with acceptor **43b** and complete consumption of the acceptor was observed after 44 h. However, the Stetter adduct could not be isolated pure. In addition to the Stetter product **45a**, the cross-benzoin product **46a** was observed in a 1:1 ratio of **45a** and **46a** as an inseparable mixture of products.



Scheme 2.3 Attempt to Expand the Scope of the Intermolecular Stetter Reaction to Aliphatic Aldehyde.

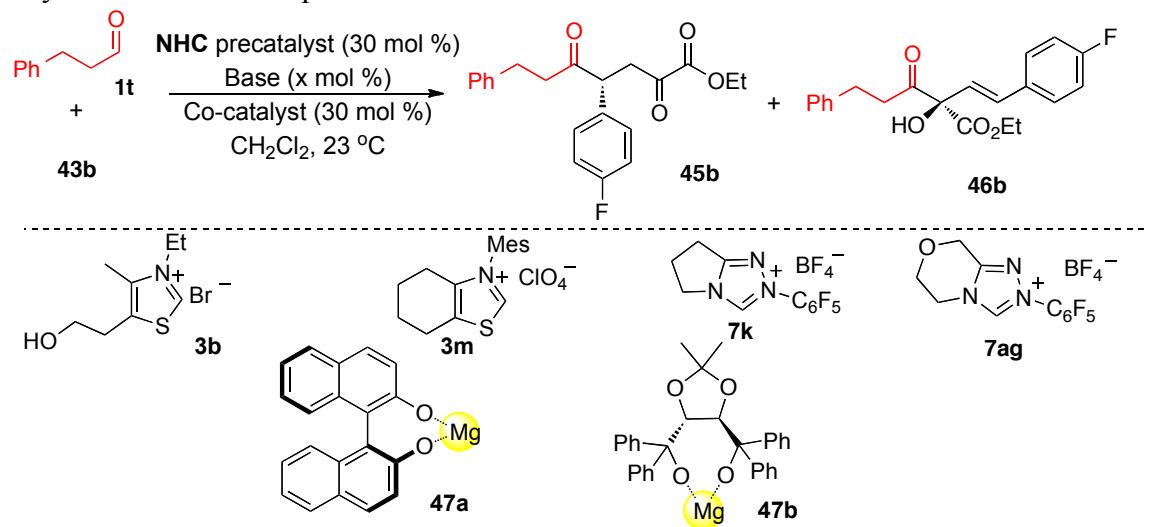
2.2.3 Preliminary Studies on the Extension of the Scope of the Stetter Reaction to Aliphatic Aldehydes

After recognizing that the optimal conditions developed for 2-heteroaromatic aldehydes are not applicable to aliphatic aldehydes, a brief screening of achiral azolium salts was performed with aliphatic aldehyde **1t** and acceptor **43b** (Table 2-5). Using achiral triazolium **7k** resulted in no reaction, whereas thiazolium salt **3b** resulted in 40% conversion to the Stetter product in excellent regioselectivity (entries 1-2). Interestingly, complete regioselectivity to the cross-benzoin product was observed when triazolium salt **7ag** was employed (entry 3). The reason for the excellent, but opposite, regioselectivity observed with NHC precursors **3b** and **7ag** is not clear at this point. However, the excellent catalyst controlled regioselectivity of the reaction (Stetter vs. cross-benzoin) warrants further investigation.

Although chiral thiazolium salts employed in the literature have resulted in poor enantioselectivity for the Stetter reaction,⁶⁵ the use of chiral magnesium complexes as co-catalysts could improve the enantioselectivity.⁶⁶ The use of achiral Mg(O*t*Bu)₂ as Lewis acid accelerated the reaction and complete consumption to the Stetter adduct was observed (entry 5). In contrast, no improvement in reactivity was observed when Mg(O*t*Bu)₂ was used as co-catalyst with triazolium salt **7k** and the reaction resulted in the

formation of numerous unidentified side products (entry 4). However, strong bases, such as DBU are required to generate the catalytic carbene species with thiazolium salt **3b**. The use of strong bases could be problematic for enantioselective transformations, as the desired Stetter product possesses an enolizable stereogenic center. As a result, thiazolium salt **3m** was explored, since the use of weak bases such as *i*Pr₂NEt was reported by Glorius and coworkers to be sufficient to generate the catalytic carbene species in benzoin reactions.⁶⁷ Gratifyingly, the reaction performed with thiazolium salt **3m** furnished the Stetter product **45b** in good conversion along with the cross-benzoin product **46b** in a 7:1 ratio (entry 6). When the reaction was performed with thiazolium salt **3m** and co-catalyst Mg(*O**t*Bu)₂, excellent regioselectivity to the Stetter product was achieved, albeit in low conversion (entry 7). Unfortunately, the use of Mg(*n*Bu)₂ and a chiral diol ligand to generate a chiral Mg complex⁶⁸ resulted in no reactivity with thiazolium **3m**, and degradation of the starting material was observed (entries 8-9). However, the promising result obtained with thiazolium salt and magnesium Lewis acid to exclusively obtain the Stetter product (entry 5) warrants further investigation with chiral Mg complexes to extend the scope of the Stetter reaction to aliphatic aldehydes.

Table 2-5 Stetter Reaction: Scope of the Reaction with Aliphatic Aldehydes and α -Aryl α -Ketoester Acceptor **43b**.^a



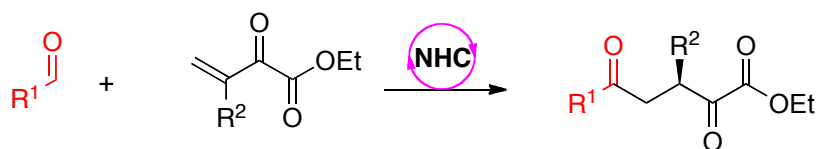
entry	NHC precatalyst	base (x mol %)	co-catalyst	time (h)	conv. (%) ^b	product ratio (45b:46b) ^d
1	7k	<i>i</i> Pr ₂ NEt (100)	-	5	<5	-
2	3b	DBU (30)	-	20	40	>20:1
3	7ag	<i>i</i> Pr ₂ NEt (100)	-	24	86	1:>20
4	7k	<i>i</i> Pr ₂ NEt (100)	Mg(<i>Or</i> Bu) ₂	6	<5 ^d	-
5	3b	DBU (30)	Mg(<i>Or</i> Bu) ₂	2.5	>95	>20:1
6	3m	<i>i</i> Pr ₂ NEt (100)	-	6	75	7:1
7	3m	<i>i</i> Pr ₂ NEt (100)	Mg(<i>Or</i> Bu) ₂	6	38	>20:1
8	3m	<i>i</i> Pr ₂ NEt (100)	47a	20	<5	-
9	3m	<i>i</i> Pr ₂ NEt (100)	47b	20	<5	-

^a Unless otherwise noted, all reactions were performed by the addition of base to a solution of acceptor **43b** (1 equiv.), aldehyde **1t** (1.5 equiv.), and precatalyst in dichloromethane (0.2 M) at 23 °C. ^b Conversion determined by ¹H NMR analysis of the crude reaction mixture. ^c Product ratio was determined by ¹H NMR analysis of the crude reaction mixture. ^d Reaction resulted in a complex mixture.

2.2.4 Preliminary Studies on the Extension of the Scope of the Stetter Reaction to β -Substituted β,γ -Unsaturated- α -Ketoester Acceptors

Glorius and coworkers have recently reported a highly enantioselective α -protonation for the generation of α -amino ester derivatives through a Stetter reaction (Scheme 1.25, page 22). The use of terminal alkenes has allowed ‘acyl anion’ equivalents derived from sterically-demanding aryl aldehydes to undergo conjugate additions.⁴⁶

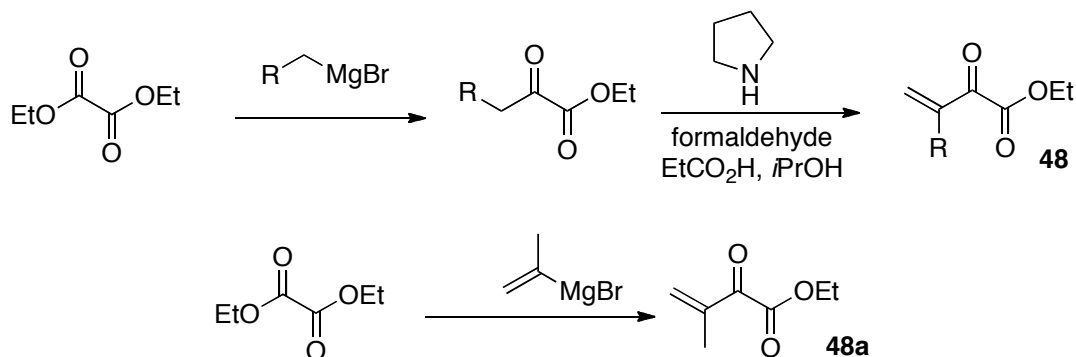
Following the success with using γ -aryl substituted β,γ -unsaturated- α -ketoester acceptors for the Stetter reaction, the methodology could potentially be extended to the use of β -alkyl β,γ -unsaturated- α -ketoester acceptors. The successful implementation of this methodology would give access to enantiomerically-enriched β -alkyl α -ketoesters (Scheme 2.4).



Scheme 2.4 Proposed Intermolecular Stetter Reaction with β -Alkyl β,γ -Unsaturated α -Ketoester Acceptors.

The traditional enolate-based methods using chiral auxiliaries to access α -alkyl carbonyl moieties require stoichiometric amounts of the chiral reagent.⁶⁹ In addition, highly activated alkylating agents are typically required for the reaction to proceed. In contrast to the use of chiral auxiliaries, β -alkyl α -ketoester moieties could, in principle, be obtained catalytically through an NHC-catalyzed intermolecular Stetter reaction, featuring a diastereoselective α -protonation under mild conditions. To investigate the

potential of β -alkyl α -ketoesters for the Stetter reaction, acceptors **48** are synthesized in 1 or 2 steps, as shown in Scheme 2.5.



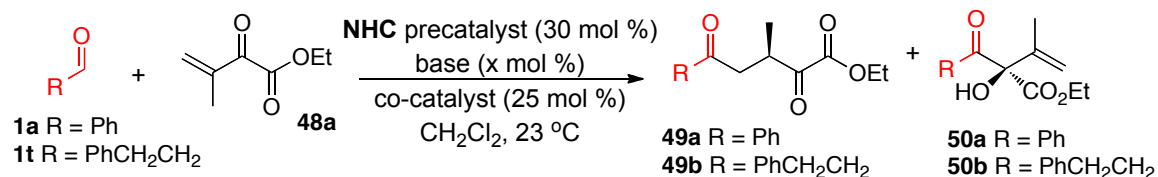
Scheme 2.5 Synthetic Routes to Access β -Alkyl Substituted α -Ketoester Acceptors.

Employing achiral triazolium salt **7k** for the Stetter reaction with benzaldehyde **1a** and terminal alkene acceptor **48a** resulted in no reaction (Table 2-6, entry 1). Attempts to activate the acceptor through the use of Lewis acids, such as $Mg(OtBu)_2$ did not furnish the desired Stetter product, nor was the cross-benzoin product observed (entry 2). The reaction with magnesium as co-catalyst also resulted in the formation of many unidentified side products. Using thiazolium salt **3b** resulted in rapid conversion to the Stetter and cross-benzoin products (3.7:1). The difference in reactivity was presumably a result of the steric difference between thiazolium- and triazolium-derived carbenes.

Aliphatic aldehyde **1t** was also explored for the Stetter reaction with acceptor **48a**, catalyzed by achiral triazolium salt **7k** (entry 4). Rapid conversion of the starting materials to the Stetter and cross-benzoin products was observed, whereas no reaction was obtained when benzaldehyde was employed under the same reaction conditions (entry 1). The effect of the use of $Mg(OtBu)_2$ as the Lewis acid on the reactivity and regioselectivity of the reaction was then investigated. The use of $Mg(OtBu)_2$ did not hinder the reaction, for which comparable results in conversion and regioselectivity were

observed. Notably, the reaction failed to proceed when performed with thiazolium salt **3b**. Despite the poor diastereoselectivity observed with triazolium salt **7k**, the use of chiral catalysts belonging to the same family could be explored for the enantioselective variant of the Stetter or cross-benzoin reaction.

Table 2-6 Intermolecular Stetter Reaction with β -Alkyl Substituted β,γ -Unsaturated α -Ketoester Acceptors.^a

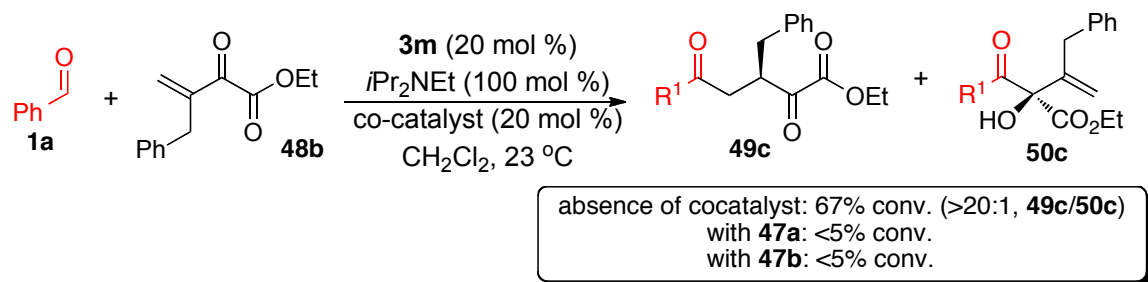


entry	aldehyde	NHC pre-catalyst	base (x mol %)	co-catalyst	time (h)	conv. (%) ^b	ratio of 49:50 ^b
1	1a	7k	<i>i</i> Pr ₂ NEt (100)	-	27	<5	-
2	1a	7k	<i>i</i> Pr ₂ NEt (100)	Mg(<i>O</i> <i>t</i> Bu) ₂	20	<5 ^c	-
3	1a	2b	DBU (30)	-	5	>95	3.7:1
4	1t	7k	<i>i</i> Pr ₂ NEt (100)	-	27	>95	1:1.6
5	1t	7k	<i>i</i> Pr ₂ NEt (100)	Mg(<i>O</i> <i>t</i> Bu) ₂	20	87	1:1.3
6 ^c	1t	3b	DBU (30)	-	5	<5	-

^a Unless otherwise noted, all reactions were performed by the addition of base to a solution of acceptor **51a** (1 equiv.), aldehyde (1.5 equiv.), and precatalyst (0.30 equiv.) in dichloromethane (0.2 M) at 23 °C. ^b Determined by ¹H NMR of the crude reaction mixture. ^c Reaction resulted in a complex mixture.

As acceptor **48a** was highly volatile and difficult to monitor by TLC, acceptor **48b** was synthesized and investigated for the Stetter reaction. Complete regioselectivity to the Stetter product was observed when the reaction was performed with thiazolium salt **3b** and benzaldehyde (not shown). As a result of this excellent observed regioselectivity,

it would be interesting to investigate the use of this family of catalysts. The achiral catalyst could be used in conjunction with chiral Lewis acids for the asymmetric variant of the Stetter reaction with aryl aldehydes and acceptor **48** to access β -alkyl α -ketoester Stetter products **49**. As a consequence of the need to use strong bases such as DBU for the transformation catalyzed by thiazolium **3b**, Glorius' thiazolium **3m** was explored. This aryl-substituted thiazolium salt is more acidic than **3b** and can be deprotonated with *i*Pr₂NEt, thus alleviating the concern of racemization under strongly basic conditions. The reaction resulted in excellent regioselectivity, albeit in lower conversion (Scheme 2.6). In the presence of the pre-formed chiral magnesium-complexes **47a** and **47b**, no reaction was observed and the formation of the benzoin product was also suppressed. The absence of benzoin side product suggests that the carbene catalyst is inhibited by the Mg complex.



Scheme 2.6 The Effect of Chiral Mg Complexes as Co-catalysts for the NHC-Catalyzed Stetter Reaction.

2.2.5 Synthetic Applications of the Stetter Adducts Obtained with α -Ketoester Acceptors

To illustrate the synthetic usefulness of the α -ketoester moiety derivatizations of the Stetter products were explored. Highly chemoselective reduction of the Stetter product could be achieved by employing Super-Hydride® at low temperature. Simply

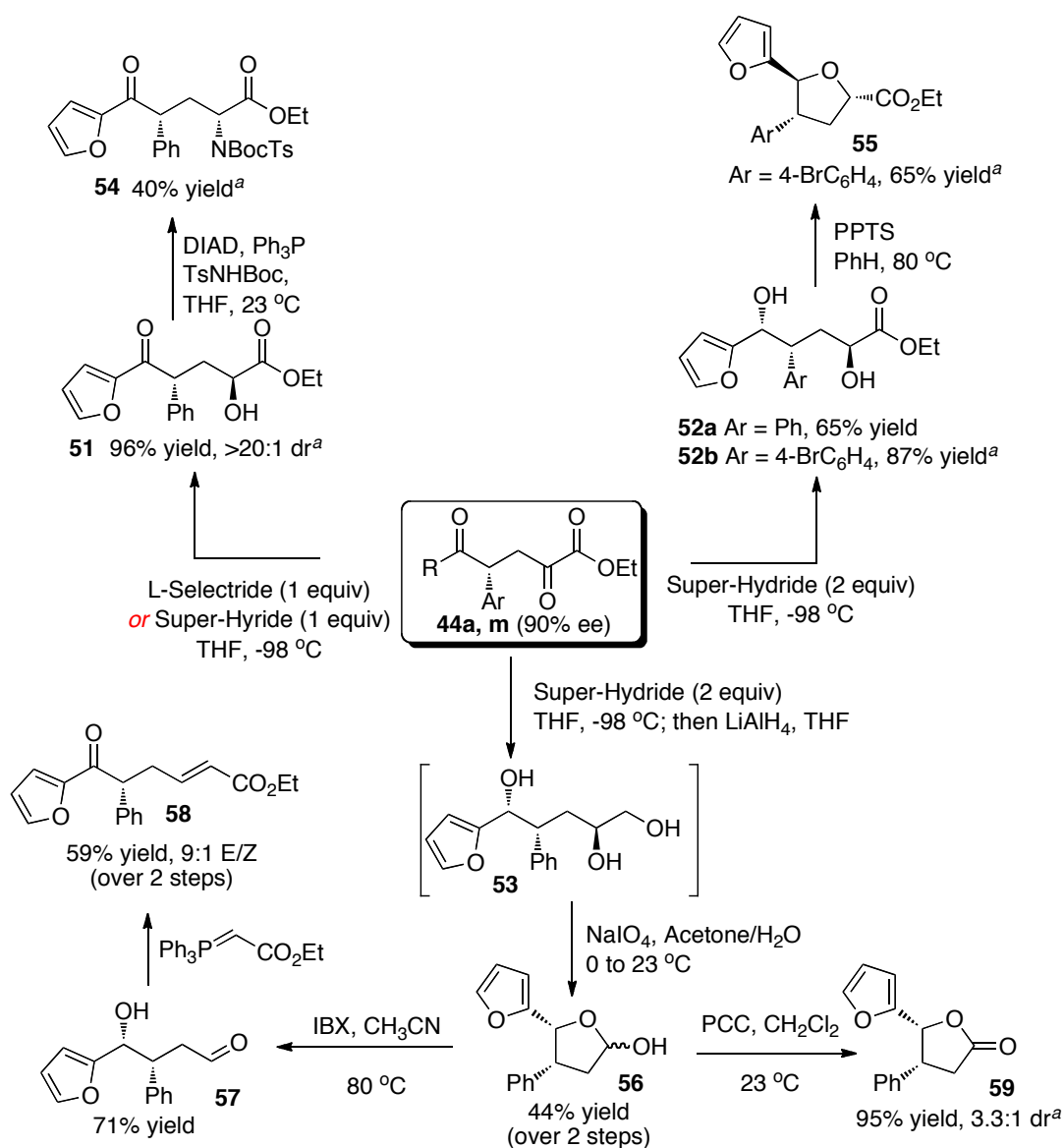
controlling the stoichiometry of the hydride source allowed access to mono-alcohol **51**, di-, and triols **52-53** in good yields, moderate to excellent diastereoselectivity, and excellent chemoselectivity (Scheme 2.7).^v

Further derivatization of the alcohol intermediates led to the synthesis of α -amino ester derivatives **54**, tetrahydrofuran derivative **55**,^{vi} α,β -unsaturated ester **58**, and lactone **59**. The relative configuration of the tetrahydrofuran derivative **55** was determined by NMR studies, which in turn allowed the assignment of the relative configuration of alcohol **51** and diol **52**.^{vii} Enantiomerically-enriched building blocks can be accessed from the Stetter products obtained with 2-heteroaromatic aldehyde and γ -aryl substituted β,γ -unsaturated- α -ketoester acceptors. Notably, oxidation of lactol **56** with IBX in acetonitrile furnished both aldehyde **57** and lactone **59** in a 3.7:1 ratio. Aldehyde **57** was then subjected to Wittig olefination to give rise to unsaturated ester **58**. Unfortunately, partial racemization occurred under the reaction conditions, as the enantiomeric excess of ester **58** was only 10% ee. The oxidation of lactol **56** was speculated to be the problematic step due to the requirement of heating and the mildly acidic nature of the oxidant. Under milder oxidizing conditions, such as using IBX in DMSO at ambient temperatures or the use of Dess-Martin periodinane, complete conversion to lactone **59** was obtained and no aldehyde product **57** was observed.

^v The formation of other alcohol products due to poor chemoselectivity was not observed in the ¹H NMR crude reaction mixture.

^{vi} Reaction sequence to access α -amino ester and tetrahydrofuran derivatives was performed by Eduardo Sánchez-Larios.

^{vii} NMR studies to determine the relative configuration of tetrahydrofuran derivative **55** and lactone **59** and the extrapolation to the relative configuration of **51** and **52** were performed by Eduardo Sánchez-Larios.

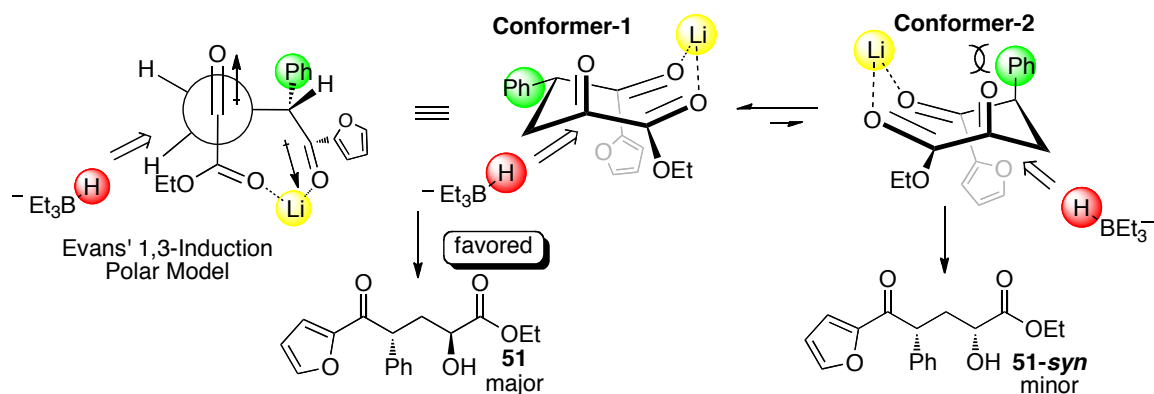


^a Reaction was performed by Eduardo Sánchez-Larios

Scheme 2.7 Synthetic Applications of the Products Obtained from the Enantioselective Intermolecular Stetter Reactions of γ-Aryl-β,γ-Unsaturated-α-Ketoesters.

The lithium counterion appears to play an essential role in the excellent diastereoselectivity observed in the reduction of **44a** with Super-Hydride® and L-Selectride®. Whereas reactions performed with N-Selectride® resulted in poor diastereoselectivity (3:1 dr), those performed with L-Selectride resulted in excellent

diastereoselectivity (>20:1 dr).^{viii} In view of the importance of the lithium counterion on the diastereoselective mono-reduction of the Stetter product **44a**, the reaction is rationalized to proceed through a closed 8-membered ring transition state. The two most Lewis basic carbonyl's of the Stetter adduct was proposed to chelate through the lithium counterion. Following Evans' model, chelation of the ester and furyl ketone moieties results in opposing dipoles for the reactive ketone and γ -polar substituent (Figure 2.2).⁷⁰ As a result of this dipole-dipole minimization, the polar γ -substituent of the reactive ketone carbonyl of the α -ketoester is oriented antiperiplanar to the carbonyl moiety. The triethyl borohydride reducing agent is speculated to approach the most stable conformer from the equatorial position to minimize an unfavorable 1,3-diaxial interaction. Conformer-2 displays a phenyl substituent in a pseudo-axial orientation and would thus be disfavoured over conformer-1 due to the unfavourable interaction between the phenyl group and the ketone, therefore forming **51** as the major diastereomer. The moderate selectivity observed for the reduction of the δ -ketone could be rationalized with a Felkin-Anh model (Figure 2.3). The role of the lithium counterion was proposed to chelate the alkoxide and the carbonyl ester moiety to form a five-membered ring.



^{viii} Reduction with N-Selectride was performed by Eduardo Sánchez-Larios.

Figure 2.2 Rationale for the Highly Diastereoselective Reduction of the α -Carbonyl of α -Ketoester Substrate **44a** using a Closed Chair-like Transition State Model.

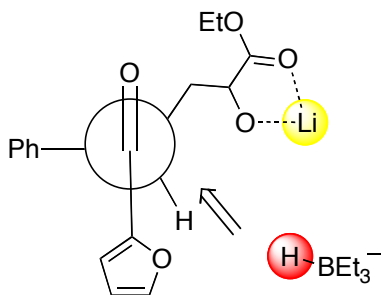
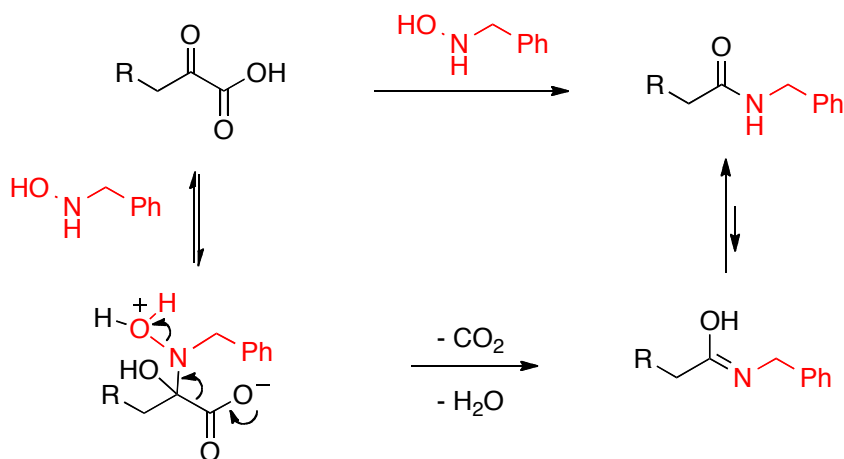
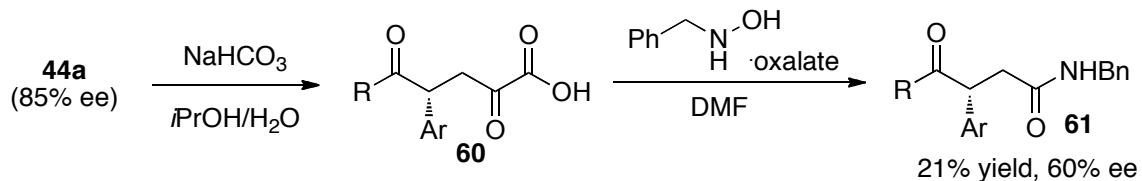


Figure 2.3 Rationale for the Stereochemical Outcome of the Reduction of the δ -Carbonyl of Stetter Adduct **44a** for the Synthesis of Diol **55** using Felkin-Anh Model.

Very recently, Bode and coworkers have reported an efficient method for the formation of amide bonds through a decarboxylative condensation of α -ketoacids with hydroxylamines (Scheme 2.8).⁷¹ Notably, the peptide coupling could be performed without racemization under their conditions. This attractive methodology would allow the conversion of the Stetter product **44a** to amide product **61**, which would be a result of a formal Stetter reaction on an α,β -unsaturated amide acceptor. As a consequence of the poorly electrophilic nature of α,β -unsaturated amides, they are currently not viable acceptors for the intermolecular Stetter reaction. Hydrolysis of the α -ketoester Stetter product **44a** was more challenging than initially anticipated. Under either acid- or base-mediated hydrolysis of the ester moiety to access α -ketoacid **60**, erosion of the enantiomeric excess of the product was observed. The best result obtained was achieved under mildly basic conditions using sodium bicarbonate, followed by decarboxylative condensation with benzyl hydroxylamine oxalate to furnish the amide product **61** in 21% yield and 60% ee (Scheme 2.9).

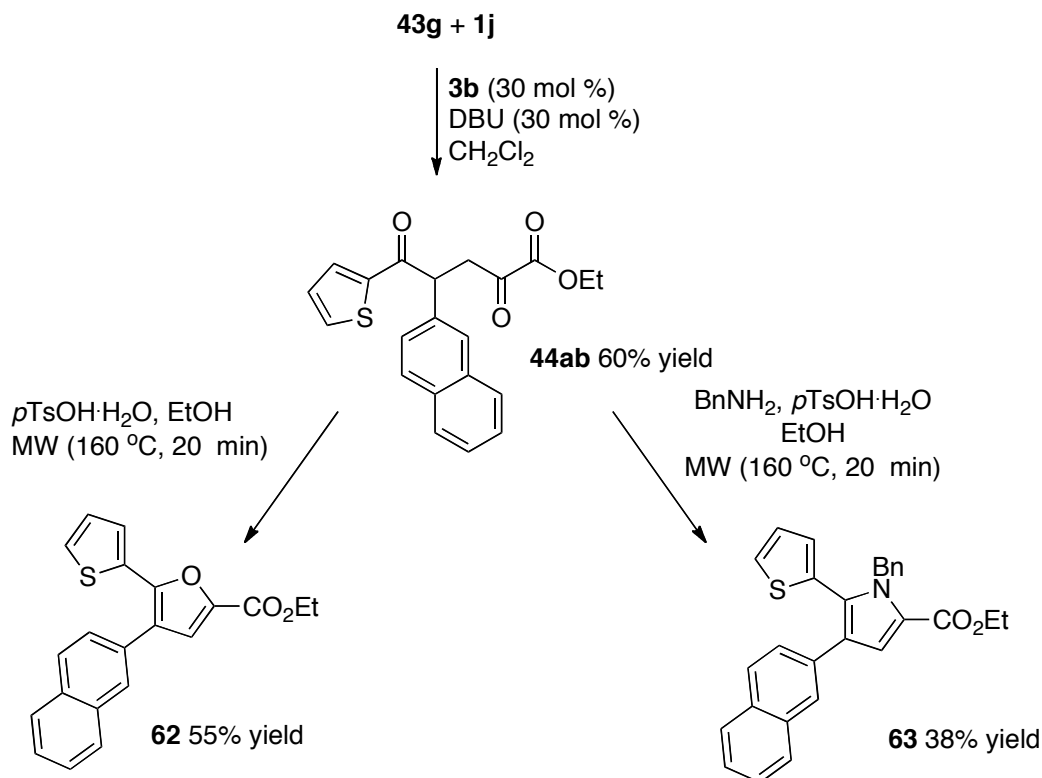


Scheme 2.8 Bode's Proposed Mechanism for the Decarboxylative Condensation of *N*-Alkylhydroxylamines and α -Ketoacids.



Scheme 2.9 Transformation of Stetter Adduct **44a** into Amide Derivative **61**.

As was first described by Müller and Scheidt, 1,4-dicarbonyl Stetter products can be converted to furan and pyrrole derivatives through a Paal-Knorr condensation reaction.⁷² Using a racemic mixture of Stetter product **44ab** trisubstituted furan and pyrrole derivatives bearing an ester moiety can be accessed in moderate yields under acidic conditions and microwave irradiation (Scheme 2.10).



Scheme 2.10 Derivatization of Stetter Product **44ab** to Trisubstituted Furan and Pyrrole.

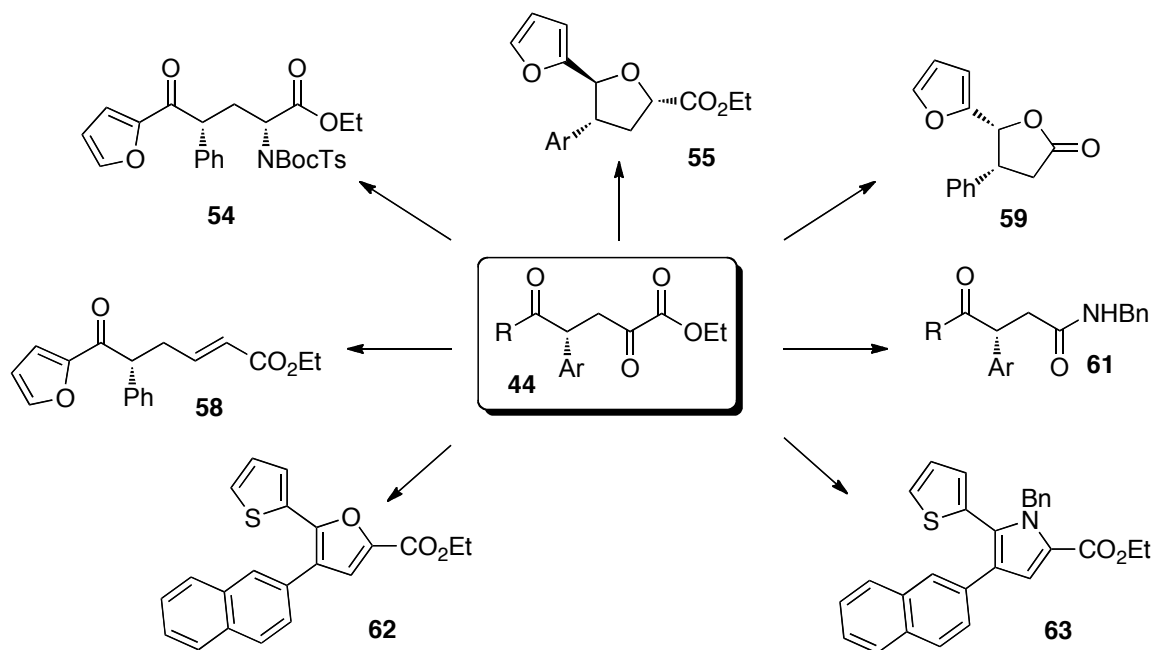
2.3 Conclusion

A highly enantioselective intermolecular Stetter reaction was developed with γ -aryl- β,γ -unsaturated- α -ketoester and 2-heteroaromatic aldehydes.⁷³ In addition to 2-heteroaromatic aldehydes, the use of aryl aldehydes such as benzaldehyde has led to good enantioselectivity in the presence of Mg(O*t*Bu)₂ as the co-catalyst for the transformation, albeit in low yields. Although low yielding, this methodology represents the first example of a highly enantioselective intermolecular Stetter reaction with aryl aldehydes and β -substituted acceptors.

Attempts to expand the scope of the reaction to aliphatic aldehydes have resulted in the formation of both the Stetter and cross-benzoin products. However, the Stetter

product could be obtained selectively through careful selection of NHC precatalysts. Promising results obtained with $\text{Mg}(\text{OtBu})_2$ and thiazolium salt **3m**, suggest the possibility of accomplishing an asymmetric variant of the Stetter reaction through the use of chiral Lewis acid complexes in conjunction with readily available achiral thiazolium salts. Furthermore, β -alkyl α -ketoester acceptors **48** were shown to be potentially useful for the Stetter reaction with aliphatic aldehydes. The successful implementation of this methodology could serve as a synthetically useful tool to access enantiomerically-enriched α -alkylated carbonyl compounds.

The synthetic usefulness of the Stetter products obtained from the α -ketoester acceptors was illustrated. Highly chemoselective reduction of the carbonyl moieties could be achieved, in addition, the alcohol products obtained could be further derivatized into α -amino esters, tetrahydrofurans, α,β -unsaturated esters, lactones, amides, furans, and pyrroles.



Scheme 2.11 Synthetic Applications of the Stetter Adduct obtained from β -Aryl Substituted β,γ -unsaturated α -ketoesters.

CHAPTER 3: NHC-CATALYZED INTERMOLECULAR CROSS-BENZOIN REACTION

Despite recent advances in the cross-benzoin reaction, control of chemo- and enantioselectivity still remains elusive. Although highly enantioselective intermolecular homo-coupling of aldehydes had been achieved, the study of chemo- and enantioselective cross coupling of different aldehydes and the coupling of aldehydes with ketones still remains in its infancy. To this date, there are only two reports of the enantioselective version of the intermolecular aldehyde-ketone cross-benzoin reaction and only moderate to good enantioselectivity was obtained. Good reactivity and enantioselectivity were achieved with 2-furaldehyde and other heteroaromatic aldehydes (Scheme 1.15, page 14). However, the only example using aliphatic aldehydes resulted in only moderate reactivity and enantioselectivity under Connon's conditions (Scheme 1.16, page 15).²⁴

3.1 Research Objective

During the course of our studies on the scope of the Stetter reaction with α -ketoester acceptors, we discovered that the use of aliphatic aldehydes gave rise to the Stetter products and the corresponding cross-benzoin products in a ca. 1:1 ratio (Scheme 2.3, page 42). Intrigued by the formation of the cross-benzoin product, we sought to further investigate α -ketoester acceptors in the aldehyde-ketone cross-benzoin reaction. Furthermore, we were interested in expanding the scope of the benzoin reaction by developing a highly enantioselective cross-benzoin reaction with aliphatic aldehydes. The successful implementation of the cross-benzoin reaction with α -ketoester acceptors would give access to enantiomerically-enriched tertiary alcohols, an important motif in

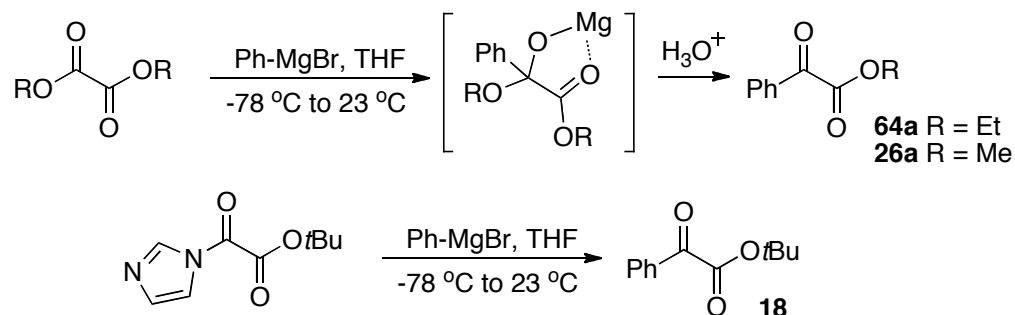
the synthesis of natural products.⁷⁴ The α -hydroxy esters generated through this method could also serve as useful building blocks for the synthesis of natural products.

3.2 α -Ketoesters As Useful Acceptors for the Aldehyde-Ketone Cross-Benzoin

Reaction: α -Aryl α -Ketoesters

3.2.1 *Synthesis of Starting Materials for the Aldehyde-Ketone Cross-Benzoin Reaction*

To avoid the formation of the inseparable Stetter adduct from the cross-benzoin product, α -ketoester acceptor **64a** was used for preliminary studies. The substrate could be accessed in one step from the Grignard addition onto diethyl oxalate (Scheme 3.1). The tetrahedral intermediate formed during the reaction was presumably stabilized through magnesium chelation with the ester moiety, thus preventing the formation of the double addition product.⁷⁵ The same approach could be applied to access methyl α -ketoester **26a** by employing dimethyl oxalate, as well as various other aryl- and alkyl-substituted α -ketoester acceptors.⁷⁶ *Tert*-butyl α -ketoester **18** was synthesized from *tert*-butyl 2-(1*H*-imidazol-1-yl)-2-oxoacetate, according to a literature precedent.⁷⁷



Scheme 3.1 Synthetic Route to Access α -Phenyl α -Ketoester Substrates.

3.2.2 Optimization of the Reaction

Gratifyingly, efficient cross-benzoin transformation of aliphatic aldehyde **1t** with α -ketoester acceptor **64a** occurred in 63% yield after 24 h with achiral triazolium salt **7k** at 30 mol % catalytic loading (Table 3-1, entry 1). A catalyst screening revealed electron-deficient morpholinone-derived salt **7ae** to be the superior precatalyst for the aldehyde-ketone cross-benzoin reaction (entry 7). Triazolium salts **7af**, **7u**, **7q**, and **7w**, which were superior catalysts for the intermolecular Stetter reaction, proved to be far less effective than morpholinone-derived **7ae** for this transformation (entries 2-5). The use of Rovis' precatalyst **7t** resulted in poor yield and poor enantioselectivity (entry 6). A solvent and base screening was performed with catalyst **7ae**, but no improvement in the yield of the reaction was observed (entries 8-13). Despite much effort, further improvement in the yield of the reaction could not be achieved without compromising the enantioselectivity (entries 14-16). Reactions were performed with various additives (not shown), such as catechol (1 equiv., 24% conv.) and $\text{Mg}(\text{OtBu})_2$ (0.1 equiv., 41% conv., 71% ee), or at longer reaction times. However, no improvements in the conversion were observed ($t = 72$ h, 65% conv., 87% ee). Furthermore, the conversion obtained from the reaction performed in dichloromethane (entry 7) ranged from 26 to 62% conversion when repeated, which could be a consequence of the moisture present in the reaction mixture (not shown). When powdered 4Å molecular sieves were employed, the conversion of the reaction was more reproducible (64-71% conversion), the product was isolated in 73% yield (entry 17). However, the enantiomeric excess of the cross-benzoin product dropped from 89 to 87% ee.

Based on the success observed with triazolium salt **7ae**, bulky morpholinone-derived precatalysts **7ah** bearing a bulky isopropyl substituent was designed and synthesized to further improve the enantioselectivity of the reaction. Improvements in the enantioselectivity of the reaction were observed with triazolium salt **7ah**, albeit with a lower yield (entry 19). On the other hand, triazolium salt **7ai** did not furnish the desired cross-benzoin product nor was the homo-benzoin product observed, presumably due to the increased steric hindrance (entry 18). The reaction was repeated with precatalyst **7ah** under the newly established reaction conditions, employing molecular sieves and moderate yield of the cross-benzoin product was obtained in high enantiomeric excess (entry 20).

Table 3-1 Optimization of the Enantioselective Aldehyde-Ketone Cross-Benzoin Reaction.^a

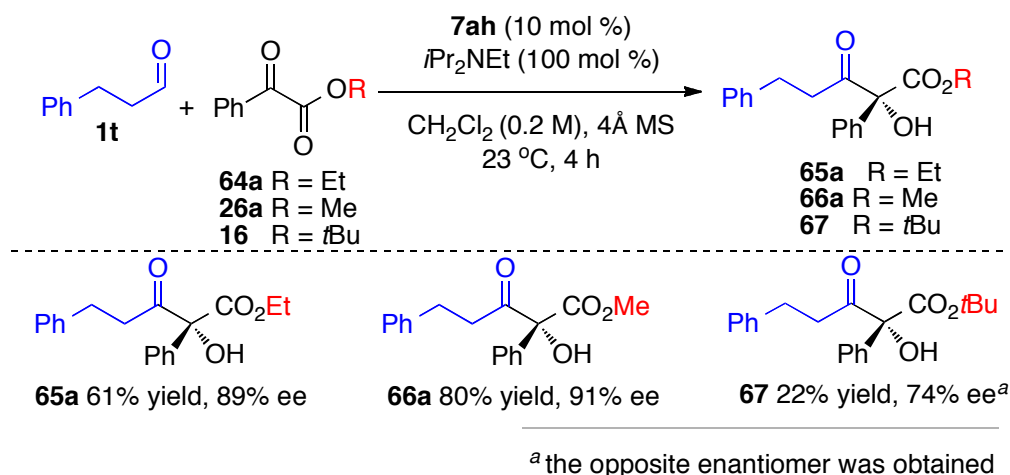
entry	NHC precatalyst (x mol %)	base (y mol %)	solvent	time (h)	yield (%) ^b	ee (%) ^c
1	7k (30)	<i>i</i> Pr ₂ NEt (100)	CH ₂ Cl ₂	24	63	-
2	7af (10)	<i>i</i> Pr ₂ NEt (100)	CH ₂ Cl ₂	3.5	77	80
3	7u (10)	<i>i</i> Pr ₂ NEt	CH ₂ Cl ₂	8	56	68

4	7q (10)	(100) <i>i</i> Pr ₂ NEt	CH ₂ Cl ₂	8	22	65 ^d
5	7y (10)	(100) <i>i</i> Pr ₂ NEt	CH ₂ Cl ₂	8	7	85
6	7t (10)	(100) <i>i</i> Pr ₂ NEt	CH ₂ Cl ₂	4	22	62 ^d
7	7ae (10)	(100) <i>i</i> Pr ₂ NEt	CH ₂ Cl ₂	4	55	89
8	7ae (10)	(100) <i>i</i> Pr ₂ NEt	THF	4	(26% conv.)	nd
9	7ae (10)	(100) <i>i</i> Pr ₂ NEt	PhMe	4	(21% conv.)	nd
10	7ae (10)	(100) <i>i</i> Pr ₂ NEt	ClCH ₂ CH ₂ Cl	4	(27% conv.)	nd
11	7ae (10)	(10) DBU	CH ₂ Cl ₂	4	(51% conv.)	nd
12	7ae (10)	(100) Et ₃ N	CH ₂ Cl ₂	4	(44% conv.)	nd
13	7ae (10)	(100) Cs ₂ CO ₃	CH ₂ Cl ₂	4	0	-
14 ^e	7ae (10)	(100) <i>i</i> Pr ₂ NEt	CH ₂ Cl ₂	4	48	nd
15 ^f	7ae (10)	(100) <i>i</i> Pr ₂ NEt	CH ₂ Cl ₂	4	51	76
16	7ae (20)	(100) <i>i</i> Pr ₂ NEt	CH ₂ Cl ₂	4	60	87
17 ^g	7ae (10)	(100) <i>i</i> Pr ₂ NEt	CH ₂ Cl ₂	4	73	87
18	7ai (10)	(100) <i>i</i> Pr ₂ NEt	CH ₂ Cl ₂	8	0	-
19	7ah (10)	(100) <i>i</i> Pr ₂ NEt	CH ₂ Cl ₂	8	27	91
20 ^g	7ah (10)	(100) <i>i</i> Pr ₂ NEt	CH ₂ Cl ₂	4	61	89

^a Unless otherwise noted, all reactions were performed by the addition of the base to a solution of aldehyde **1t** (1.5 equiv.), α -ketoester **64a** (1 equiv.), and precatalyst in the indicated solvent (0.2 M concentration) under inert atmosphere at 23 °C. ^b Isolated yield. Conversion determined by ¹H NMR of the crude reaction mixture is given in parenthesis. ^c Enantiomeric excess determined by HPLC analysis on chiral stationary phase. ^d The opposite enantiomer was obtained. ^e Reaction was performed at 0.5 M concentration. ^f Reaction was performed at 40 °C. ^g Reaction was performed in the presence of powered 4Å molecular sieves (1:1 w/w with respect to substrate **64a**).

Triazolium salt **7ah** was chosen as the optimal precatalyst for the transformation, furnishing the cross-benzoin product in high enantioselectivity. Following the optimization of the reaction conditions, the effect of the ester moiety's bulk was investigated (Scheme 3.2). In hopes of improving the enantioselectivity of the reaction with NHC precatalyst **7ah**, substrate **16** bearing a bulky *tert*-butyl ester moiety was synthesized. Surprisingly, the reaction suffered from a decrease in both the reactivity and the enantioselectivity, compared to that using ethyl α -ketoester **64a**. HPLC analysis results suggested that the opposite enantiomer was obtained as the major product. These surprising results may indicate that the relative size of the ketone substituent was responsible for the enantioselectivity, and that an increase in the size of the ester moiety leads to a switch in selectivity.^{ix} With this possibility in mind, the use of a substituent smaller than the ethyl group present in **64a** was then considered. Gratifyingly, the relatively smaller methyl ester moiety underwent the reaction with an improvement in the enantioselectivity, with a yield comparable to that obtained with **64a**.

^{ix} Derivatization of the cross-benzoin product from the *t*-butyl ester to the methyl ester was attempted to confirm this observation, however, the derivatization was found to be more challenging than anticipated. Decomposition was observed under various hydrolysis conditions.



Scheme 3.2 Importance of the Substituent on the Ester Moiety of the α -Ketoester Substrate Under Optimized Conditions.

3.2.3 Scope of the Reaction

Following the optimization of the reaction, the scope of the cross-benzoin reaction was then investigated. Aliphatic aldehydes of varying chain length were investigated (Table 3-2). The use of hydrocinnamaldehyde furnished the desired cross-benzoin product in good yield and good enantioselectivity (80% yield, 91% ee, entry 1). An increase in the length of the aldehyde chain is accompanied by an increase in enantioselectivity, where acetaldehyde resulted in a significant drop in enantioselectivity (30% ee, entry 2), whereas when propanal was employed, the reaction resulted in a significant improvement in enantioselectivity. The use of butanal furnished the cross-benzoin product **66d** in excellent enantiomeric excess (91% ee, entry 4). With increasing carbon chain length, aldehydes such as octanal furnished the cross-benzoin product **66e** in excellent enantiomeric excess (93% ee, entry 5). The introduction of a substituent in the aldehyde's α - or β -position resulted in no reaction or low reactivity (entries 6-7,9). Gratifyingly, at higher catalytic loading (30 mol %) the reaction proceeded with branched

aldehyde **1w** in excellent enantioselectivity, albeit in low yield (entry 8). Acetyl protecting groups were also found to be compatible under the reaction conditions, furnishing the desired cross-benzoin product **66i** in moderate yield and excellent enantioselectivity (entry 10). The use of heteroaromatic, aromatic, and α,β -unsaturated aldehydes resulted in no reaction (entries 11-13). Most intriguingly, electron-deficient triazolium salt **7ah** as precatalyst was most effective for aliphatic aldehydes, as only trace of amounts of the homo-benzoin products were observed with furfural **1f** and aryl aldehyde **1s**, with no cross-benzoin product being formed. The absence of homo-benzoin side product suggested that the carbene catalyst could have difficulty forming the Breslow intermediate with aryl and heteroaryl aldehydes.

Table 3-2 Intermolecular Aldehyde-Ketone Cross-Benzoin Reaction: Scope of the Reaction with Various Alkyl Aliphatic Aldehydes.^a

entry	aldehyde	time (h)	product	yield (%) ^b	ee (%) ^c
1	1t	4	66a	80	91
2	1e	24	66b	88	30
3	1b	4	66c	82	91
4	1u	4	66d	92	91
5	1s	4	66e	98	93

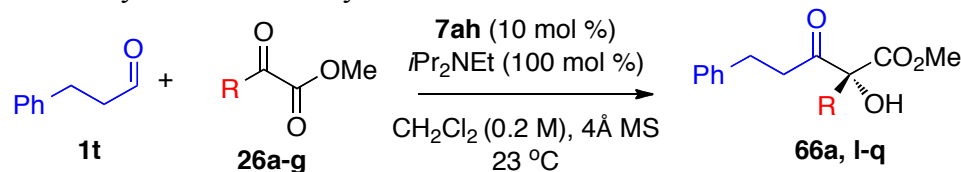
6		24	66f	0	-
7		24	66g	(13% conv.) 43 ^d	- 97 ^d
8					
9		21	66h	0	-
10		2	66i	56	94
11		24	66j	0	-
12		24	66k	0	-
13		24	66l	0	-

^a Unless otherwise noted, all reactions were performed by the addition of *i*Pr₂NEt (1 equiv.) to a solution of acceptor **68a** (1 equiv.), aldehyde **1** (1.5 equiv.), precatalyst **7ah** (0.1 equiv.), and powdered 4Å MS (1:1 w/w with respect to acceptor **68a**) in dichloromethane (0.2 M) at 23 °C. ^b Isolated yield. ^c Enantiomeric excess was determined using HPLC on chiral stationary phase. ^d Reaction was performed at 30 mol % catalytic loading of **7ah**.

Various aryl-substituted acceptors **26a-e** furnished the desired cross-benzoin products in moderate to good yield and excellent enantioselectivity (Table 3-3). However, the use of α -ketoester **26b** bearing a naphthalene substituent resulted in a decrease in enantioselectivity (85% ee, entry 1) and a significant drop in the yield of the reaction (47%); good enantioselectivity is nevertheless preserved. Similarly, when *p*-tolyl substrate **26c** was employed, the desired cross-benzoin product **66n** resulted in a decrease in reactivity and consequently, a lower yield (entry 2). However, cross-benzoin product **66n** was obtained in excellent enantioselectivity (95% ee). The added steric hindrance of the naphyl substituent and the small electron-donating effect of the methyl

substituent were presumably detrimental to the reaction rate. Electron-poor aryl substituents were then explored. Using 4-bromophenyl substrate **26d** furnished the desired cross-benzoin product **66o** in excellent yield and enantioselectivity (entry 3). On the other hand, when 3-methoxyphenyl substrate **26e** was employed, the cross-benzoin product **66p** was obtained in lower yield and good enantioselectivity (entry 4). The use of heteroaromatic substituents proved to be more challenging, despite the rapid consumption of the starting materials (entries 5-6). Indeed, the reaction employing 2-pyridyl substrate **26f** resulted in complete conversion to a racemic product (entry 5). The isolation of cross-benzoin product **66q** proved to be challenging and resulted in low yield. In contrast to the use of 2-pyridyl substrate **26f**, the use of 3-pyridyl substrate **26g** resulted in a high yield and moderate enantioselectivity (entry 6). It is apparent from these results that the steric and electronic influence of the substituent on the substrate has a crucial effect on the reactivity and stereoselectivity of the reaction. Despite the limitations of the reaction, this methodology constitutes as the first highly enantioselective intermolecular aldehyde-ketone cross-benzoin reaction.

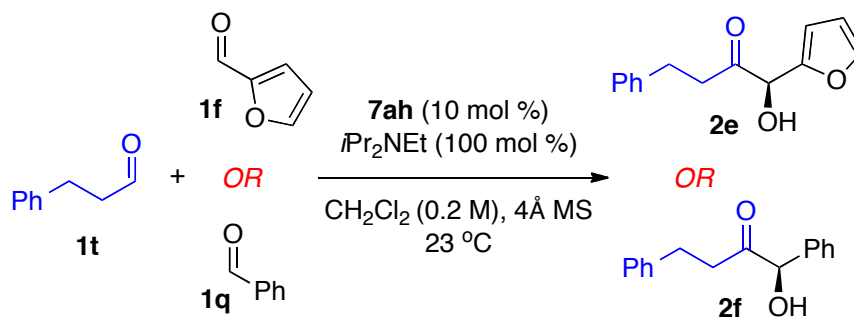
Table 3-3 Intermolecular Aldehyde-Ketone Cross-Benzoin Reaction: Scope of the Reaction with Hydrocinnamaldehyde.^a



entry	acceptor (R)	time (h)	product	yield (%) ^b	ee (%) ^c
1	26b 2-naphyl	20	66m	47	85
2	26c 4-MeC ₆ H ₄	24	66n	47	95
3	26d 4-BrC ₆ H ₄	4.5	66o	92	91
4	26e 3-(MeO)-C ₆ H ₄	5	66p	54	91
5	26f 2-Py	3.5	66q	28	0
6	26g 3-Py	2.5	66r	89	77

^a Unless otherwise noted, all reactions were performed by the addition of *i*Pr₂NEt (1 equiv.) to a solution of acceptor **26** (1 equiv.), aldehyde **1t** (1.5 equiv.), precatalyst **7ah** (0.1 equiv.), and powered 4Å MS (1:1 w/w with respect to substrate **26**) in dichloromethane (0.2 M) at 23 °C. ^b Isolated yield. ^c Enantiomeric excess was determined using HPLC on chiral stationary phase.

The lack of benzoin product formation when heteroaromatic aldehyde **1f** or aryl aldehyde **1s** was employed for the aldehyde-ketone cross-Benzoin reaction suggests that the carbene catalyst derived from triazolium salt **7ah** has difficulty forming the Breslow intermediate. The more facile Breslow intermediate formation with aliphatic aldehydes could be advantageous for the intermolecular cross benzoin reaction between aliphatic aldehydes and aromatic or heteroaromatic aldehydes (Scheme 3.3). The tendency for catalyst **7ah** to form the Breslow intermediate with aliphatic aldehydes might favour the formation of **2e** over **2f**. The chemoselectivity of the reaction would be catalyst controlled, therefore broadening the scope of the coupling partners for the cross-Benzoin reaction. Research along these lines is currently being investigated within the Gravel group.

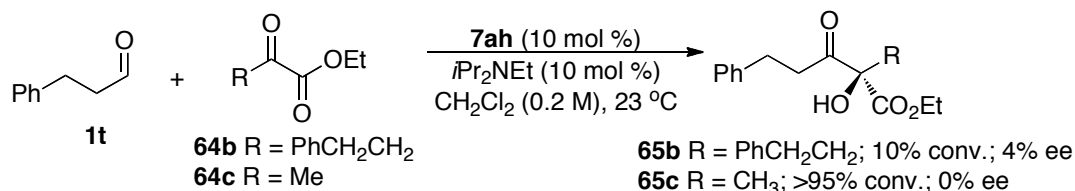


Scheme 3.3 Proposed NHC-Controlled Highly Chemoselective Cross-Benzoin Reaction.

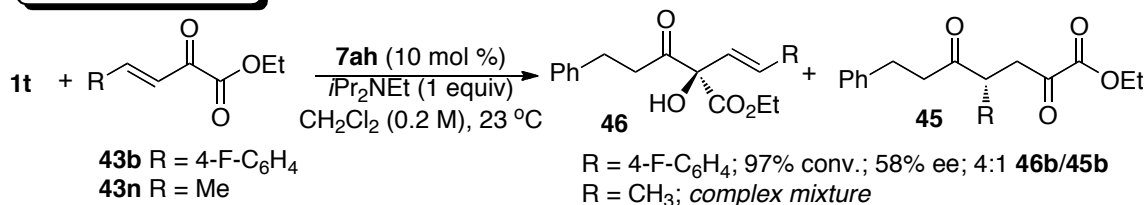
3.2.4 α -Ketoesters as Useful Acceptors for the Aldehyde-Ketone Cross-Benzoin Reaction: Alkyl-, Alkenyl-, and Alkynyl-Substituted α -Ketoesters

The use of alkenyl- and alkyl-substituted α -ketoesters resulted in good conversion under the optimized conditions for aryl substrates. However, low to poor enantioselectivity was obtained (Scheme 3.4). Using alkynyl α -ketoester substrate **64d** resulted in complete consumption of the starting material. However, only trace amounts of the desired product **65d** were observed, in addition to the formation of many unidentified side-products. Although the results obtained with acceptor **43b** were promising, a significant disadvantage with alkenyl substrates was the formation of the inseparable mixture of the cross-benzoin and the Stetter products. From the results obtained, it was recognized that separate optimization of the reaction conditions were required in order to extend the scope of the reaction to aliphatic and alkenyl substrates.

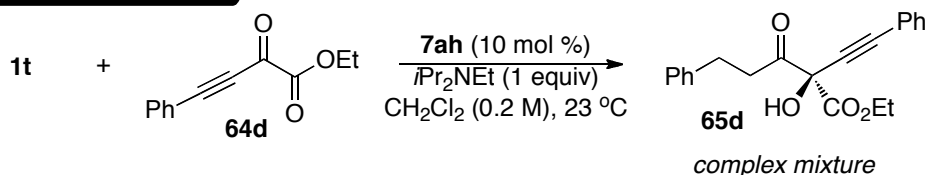
Aliphatic α -Ketoesters



Alkenyl α -Ketoesters



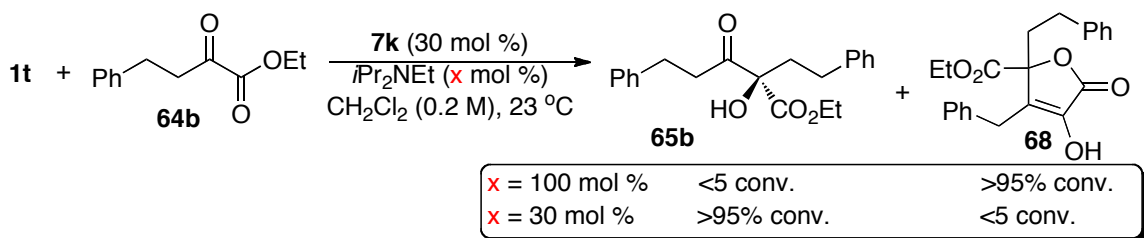
Alkynyl α -Ketoesters



Scheme 3.4 Intermolecular Aldehyde-Ketone Cross-Benzoin Reaction of Aliphatic Aldehydes with Aliphatic α -Ketoester **64b-c**, Alkenyl α -Ketoester **43b,n** and Alkynyl α -Ketoester **64d**.

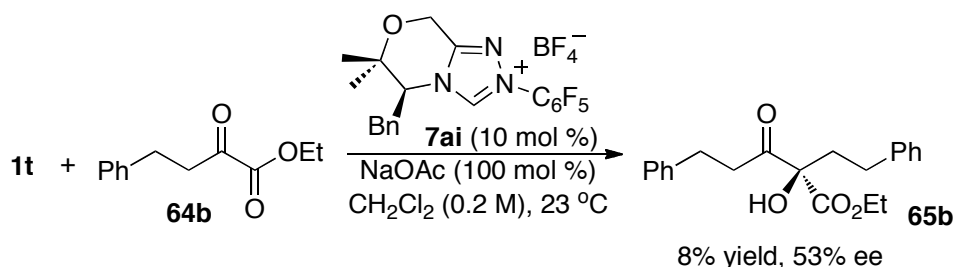
3.2.5 Preliminary Studies on the Extension of the Scope of the Reaction to Alkyl and Alkenyl α -Ketoester Substrates

At the outset, it was envisaged that the acidity of β -protons in alkyl-substituted α -ketoesters could be a problem under the basic conditions used in the cross-benzoin reaction. Indeed, the amount of base was found to be crucial, as excess amounts of base led to the aldol condensation of the substrate (Scheme 3.5). Gratifyingly, using catalytic amounts of the base with achiral triazolium salt **7k** led to the desired cross-benzoin product in good yields, whereas excess base led to the dimerization of the acceptor **64b**.



Scheme 3.5 The Importance of the Amount of Base in Intermolecular Cross Aldehyde-Ketone Reaction between Aliphatic α -Ketoesters and Aliphatic Aldehydes.

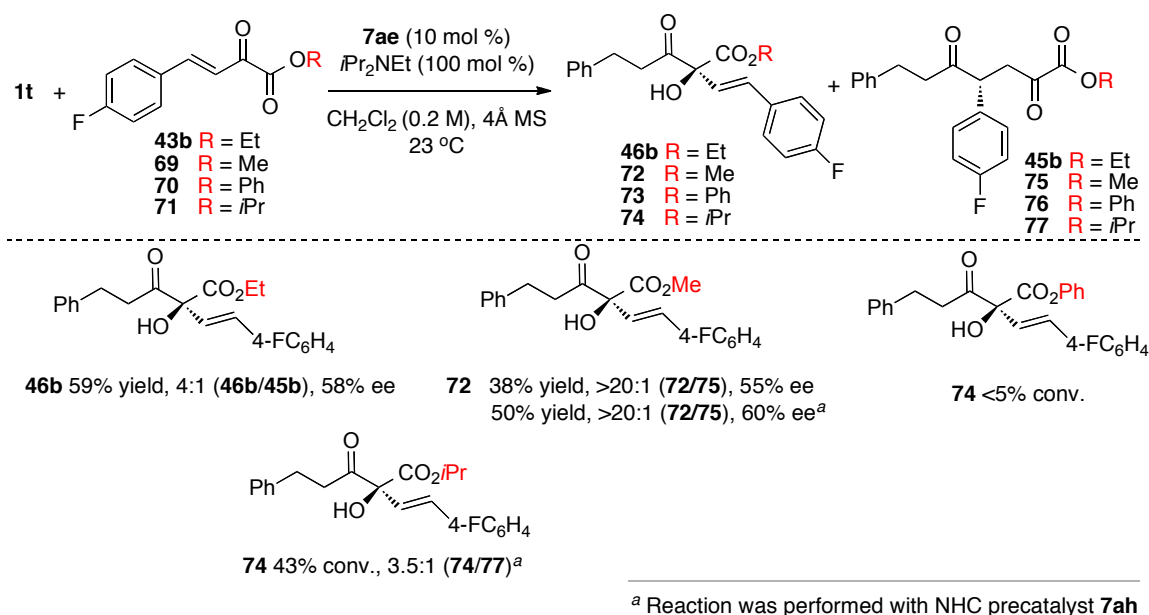
Despite extensive catalyst screening, the best result obtained thus far was the poor reactivity and poor enantioselectivity obtained with triazolium salt **7ai** (8% yield, 53% ee, Scheme 3.6). The use of ethyl pyruvate **64c** resulted in excellent conversion and good yield of the corresponding cross-benzoin product. However, the product obtained from this reaction was found to be racemic (Scheme 3.4). No improvement in the enantiomeric excess was obtained despite an extensive catalyst screening.



Scheme 3.6 Intermolecular Cross-Benzoin Reaction of Hydrocinnamaldehyde with Alkyl α -Ketoester **64b**.

Under reaction conditions optimized for aryl-substituted α -ketoester substrates, triazolium precatalyst **7ae** was investigated with alkenyl α -ketoester **43b**. The use of alkenyl substrate **43b** and hydrocinnamaldehyde resulted in moderate regioselectivity (4:1, **46b/45b**, Scheme 3.7) and moderate enantioselectivity (58% ee). Replacing the ethyl ester moiety with a methyl ester resulted in complete regioselectivity to the cross-benzoin product **72**. No cross-benzoin nor Stetter product was observed with phenyl ester substrate **70**. Triazolium precatalyst **7ah** was then explored with alkenyl substrate

69. Gratifyingly, improvements in the yield and the enantioselectivity of the cross-benzoin product were achieved in excellent regioselectivity. Unfortunately, the regioselectivity of the reaction significantly decreases when the methyl ester moiety is replaced with a bulky isopropyl ester. Taken together, these results indicate that the bulk of the ester moiety plays an important role in the regioselectivity of the coupling between aliphatic aldehydes and β,γ -unsaturated- α -ketoesters. After determining that methyl α -ketoester substrates were ideal for the transformation, further optimization of the reaction conditions was performed with triazolium precatalyst **7ah**.

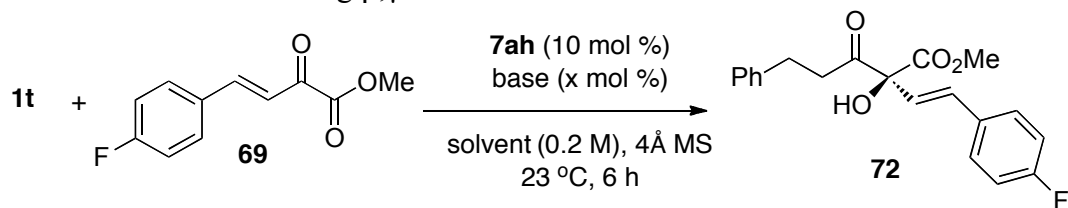


Scheme 3.7 Effect of the R Group on the Ester Moiety of Alkenyl-Substituted α -Ketoesters in the Aldehyde-Ketone Cross-Benzoin Reaction.

A solvent screening was performed to reveal dichloromethane as the optimal solvent (Table 3-4, entries 1-4). The use of weaker base sodium acetate resulted in both poor reactivity and poor enantioselectivity (entry 5). Surprisingly, in contrast to when $i\text{Pr}_2\text{NEt}$ was used as the external base, the use of triethylamine furnished the cross-benzoin product in moderate yield and improved enantioselectivity (entry 6). $\text{Mg}(\text{O}t\text{Bu})_2$

was used as a Lewis acid co-catalyst in hopes to improve the enantioselectivity of the reaction, an effect previously observed for the Stetter reaction. However, the Lewis acid appears to be an inhibitor for the cross-benzoin reaction, as lower conversion was observed with the co-catalyst (entry 10). Moreover, no improvement in the enantiomeric excess was observed. To further improve the moderate enantioselectivity of the reaction, the catalytic loading was increased to 20 mol % with triethylamine as the optimal base (entry 11). This increase in the catalytic loading resulted in the rapid conversion of the starting material to the cross-benzoin product, but no improvement in the enantiomeric excess was achieved. The rapid conversion to the cross-benzoin product was observed at ambient temperature, therefore the reaction was performed lower temperature (0 °C) in hopes to improve the enantioselectivity of the reaction (entry 12). The reaction resulted in low yield and no improvement was observed in the enantioselectivity of the reaction.

Table 3-4 Optimization of the Reaction for the Enantioselective Aldehyde-Ketone Cross-Benzoin Reaction using β,γ -Unsaturated- α -Ketoester **69**.^a

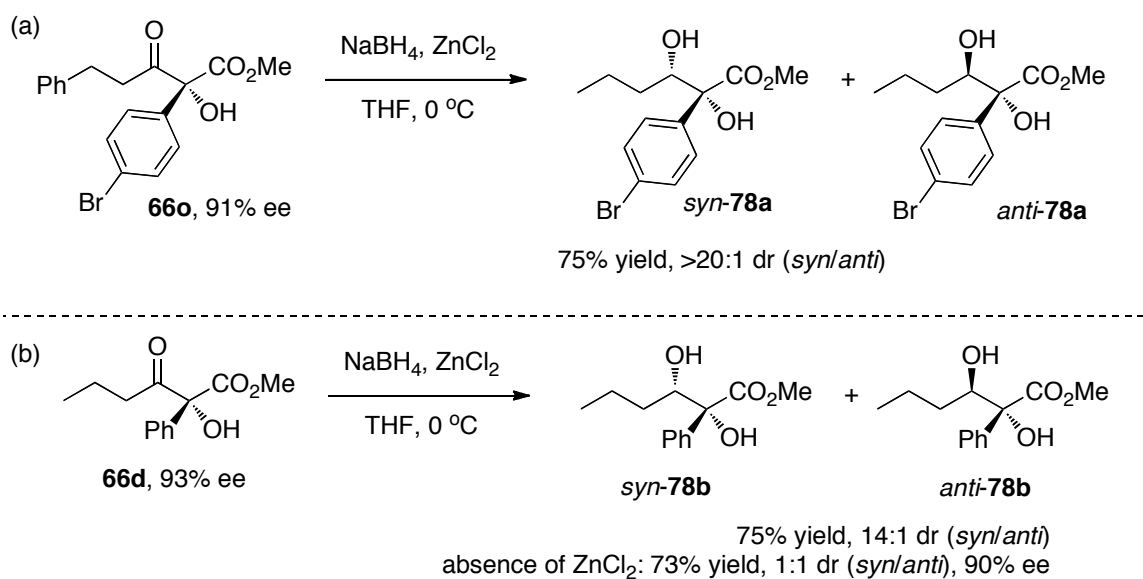


entry	base (x equiv.)	solvent	yield (%) ^b	ee (%) ^c
1	<i>i</i> Pr ₂ NEt (100)	CH ₂ Cl ₂	50	55
2	<i>i</i> Pr ₂ NEt (100)	THF	50	14
3	<i>i</i> Pr ₂ NEt (100)	toluene	46	23
4	<i>i</i> Pr ₂ NEt (100)	MeOH	0	-
5	NaOAc (100)	CH ₂ Cl ₂	9	19
6	Et ₃ N (100)	CH ₂ Cl ₂	36	68
7	Et ₃ N (100)	CH ₂ Cl ₂ (0.1 M)	34	67
8	Et ₃ N (100)	CH ₂ Cl ₂ (0.5 M)	18	64
9	Et ₃ N (100)	CH ₂ Cl ₂ (1.0 M)	0	-
10 ^d	Et ₃ N (100)	CH ₂ Cl ₂	(27% conv.)	65
11 ^e	Et ₃ N (100)	CH ₂ Cl ₂	40	67
12 ^f	Et ₃ N (100)	CH ₂ Cl ₂	30	68

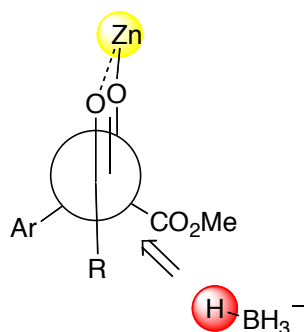
^a Unless otherwise noted, all reactions were performed by the addition of the base to a solution of aldehyde **1t** (1.5 equiv.), α -ketoester **69** (1 equiv.), and precatalyst **7ah** (0.1 equiv.) in the appropriate solvent (0.2 M) under inert atmosphere at 23 °C. ^b Isolated yield of pure product. Conversion determined by ¹H NMR of the crude reaction mixture is given in parenthesis. ^c Enantiomeric excess determined by HPLC analysis on chiral stationary phase. ^d Reaction was performed with Mg(*Or*Bu)₂ (10 mol%) as an additive. ^e Reaction was performed at 20 mol% catalytic loading of **7ah**. ^f Reaction was performed at 20 mol% catalytic loading of **7ah** at 0 °C.

3.2.6 Synthetic Application of the Cross-Benzoin Product Obtained with α -Ketoester Acceptors & Determination of Absolute Configuration

Cross-benzoin products **66o,d** were illustrated to serve as useful intermediates for the synthesis of *syn*-diols in excellent diastereoselectivity (Scheme 3.8). The presence of a chelating element was crucial for the diastereoselectivity of the reduction. When the reaction was performed with NaBH₄ in methanol, the reduction resulted in poor diastereoselectivity (Scheme 3.8b). The excellent diastereoselectivity observed with zinc chloride could be rationalized using the Cram-chelate model (Scheme 3.9). Unfortunately, the efforts to determine the absolute configuration of the product via crystallization of *syn*-diol **78a**, in various solvent combinations were not fruitful for x-ray crystallography.

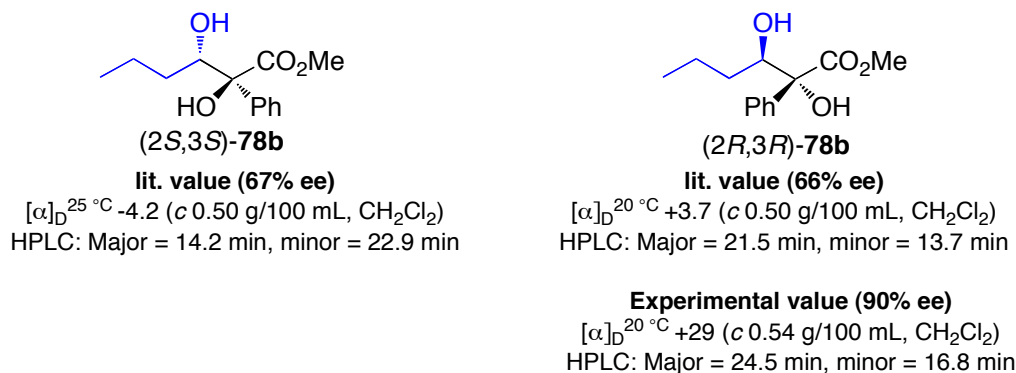


Scheme 3.8 Highly Chemoselective Reduction of Cross-Benzoin Products **66o,d** to Access *Syn*-Diols **78**.



Scheme 3.9 Using the Cram-chelate Model to Rationalize the Highly Diastereoselective Reduction of Cross-Benzoin Product **66**.

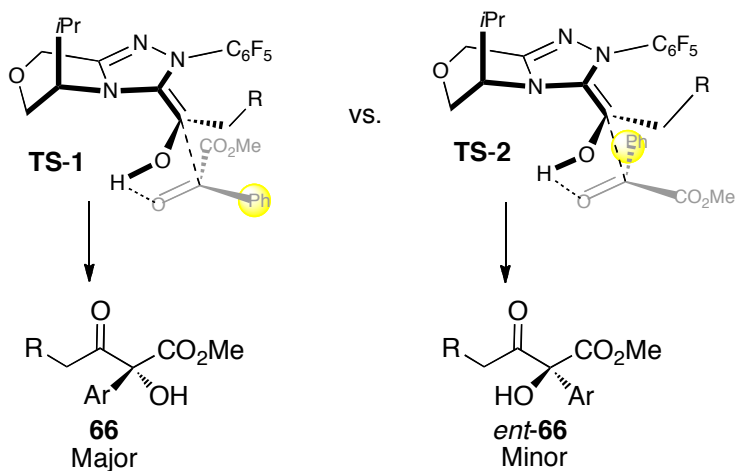
Gratifyingly, *anti*-**78b** was a known compound and both enantiomers were characterized and reported by Mahrwald and coworkers.⁷⁸ The optical rotation and the HPLC elution times of *anti*-**78b** were compared to the literature to tentatively assign the *anti*-diol **78b** obtained as the (2*R*,3*R*)-product (Scheme 3.10).



Scheme 3.10 Determination of Absolute Configuration of Cross-Benzoin Product **66**: Comparison of the Known Optical Rotation and HPLC Elution Times of *anti*-**78b**.

The stereochemical outcome of the cross-benzoin reaction was proposed to proceed through a five-membered transition state through a hydrogen bonding interaction (Scheme 3.11). The favoured transition state (**TS-1**) has the larger aryl substituent oriented away from the carbene catalyst and the smaller ester moiety under the cyclic system. Whereas, **TS-2** leading to the formation of the minor stereoisomer orients the

large aryl substituent under the bicyclic ring would thus be disfavoured due to the unfavourable steric interactions, therefore forming **66** as the major enantiomer. The low enantioselectivity observed with short carbon chain aldehyde, acetaldehyde could be attributed to the formation of both *E*- and *Z*-isomer of the Breslow intermediate.

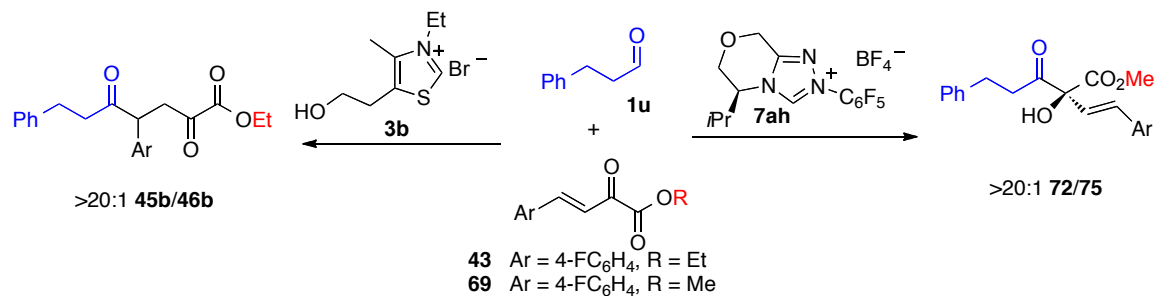


Scheme 3.11 Rationale for the Stereochemical Outcome of the Cross-Benzoin Reaction with α -aryl substituted α -Ketoesters.

3.3 Conclusion

A highly enantioselective aldehyde-ketone cross-benzoin reaction between aliphatic aldehydes and aryl substituted α -ketoester acceptors was developed. Furthermore, the cross-benzoin products were shown to be useful intermediates for the synthesis of *syn*-diols in excellent diastereoselectivity. Preliminary studies on the extension of this methodology to aliphatic and alkenyl substituted α -ketoester substrates resulted in promising results, moderate yield and moderate enantioselectivity was achieved (40% yield, 68% ee). Notably, excellent regioselectivity could be achieved through the use of methyl ester acceptor **69**. The results obtained from the preliminary studies on the Stetter and cross-benzoin reactions illustrates that each product could be

obtained in a highly regioselective manner. Through the careful selection of the carbene catalyst and modification of the ester moiety either the Stetter product **45b** or cross-benzoin product **72b** could be formed exclusively (Scheme 3.12). The development of an enantioselective variant of these reactions would significantly expand their scope, leading to the formation of useful synthetic building blocks.



Scheme 3.12 Highly Catalyst Controlled Regioselectivity for the Intermolecular Stetter and the Aldehyde-Ketone Cross-Benzoin Reaction.

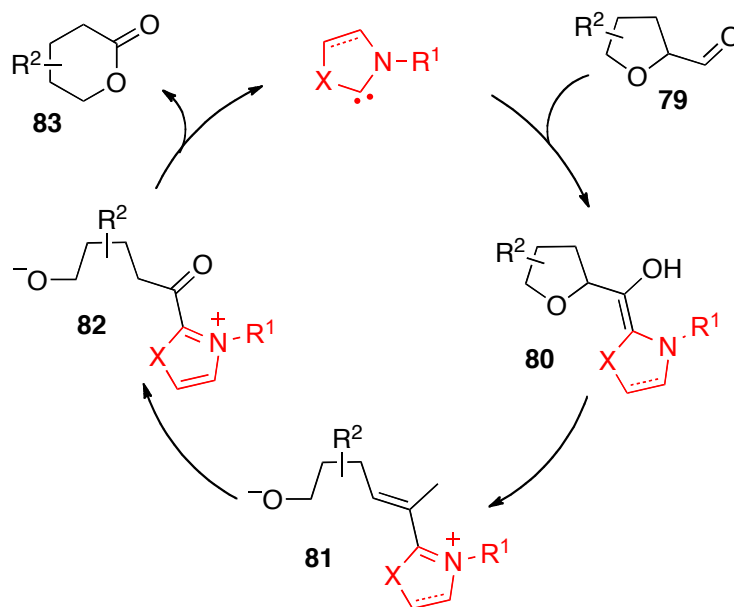
CHAPTER 4: NHC-CATALYZED RING EXPANSION REACTIONS

4.1 NHC-Catalyzed Ring Expansion of Tetrahydrofuran Derivatives to Access Lactones

The utilization of the extended umpolung to generate homoenolate and enolate equivalents and to perform internal redox transformations of α -reducible aldehydes has led to the synthesis of numerous useful building blocks. In recent years, highly diastereoselective and enantioselective ring-opening and α -elimination transformations have been achieved for the generation of carboxylic acids, ester, amide, and thioester bonds from aldehyde functionalities. One of the attractive features of this NHC-catalyzed internal redox transformation is the oxidation of aldehydes under mild, catalytic conditions.

4.1.1 *Research Objectives*

Inspired by Bode's work on the NHC-catalyzed redox transformation of epoxyaldehydes (Scheme 1.28, page 25), it was envisioned that the use of larger oxygen-containing rings would lead to the synthesis of functionalized lactones. However, the existing methodologies on the NHC-catalyzed ring-opening reactions were on strained cyclic systems, such as epoxides, aziridines and β -lactams. Thus, the ring-opening of larger cyclic rings (≥ 5) could be more challenging, however in the event that it successfully occurs, the tethering alcohol intermediate **78** would undergo a nucleophilic addition to give rise to synthetically useful lactones (Scheme 4.1).

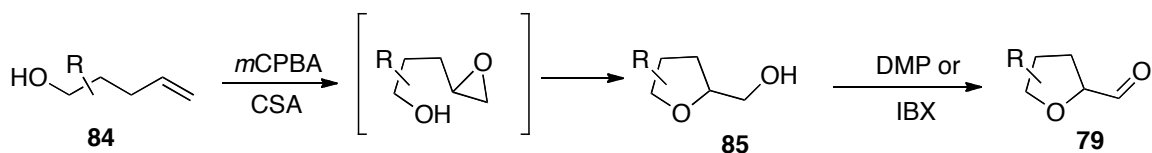


Scheme 4.1 Proposed Catalytic Cycle for the NHC-Catalyzed Ring Expansion Reaction to Access Functionalized Lactones.

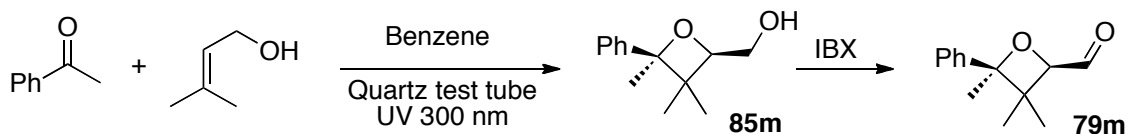
4.1.2 *Synthesis of Starting Materials*

Functionalized oxacycloalkane-2-carboxaldehydes **79** required for the investigation of the scope of the reaction could be accessed readily from the corresponding alkenols **84** in 2 steps. Epoxidation followed by spontaneous cyclization under acidic conditions gives rise to the tetrahydrofuranyl alcohols **85**. Oxidation of the alcohols could be performed with Dess-Martin periodinane or 2-iodoxybenzoic acid (IBX) (Scheme 4.2). Oxetene **79m** could be readily accessed from a [2+2] photocycloaddition of acetophenone and prenol in a very high regio- and diastereoselectivity, followed by oxidation by IBX.^{79,x}

^x Substrate **79m** was prepared by Li Wang.



Scheme 4.2 Synthetic Route to Access Substituted Oxacycloalkane-2-carboxaldehydes for the NHC-Catalyzed Ring Expansion Reaction.



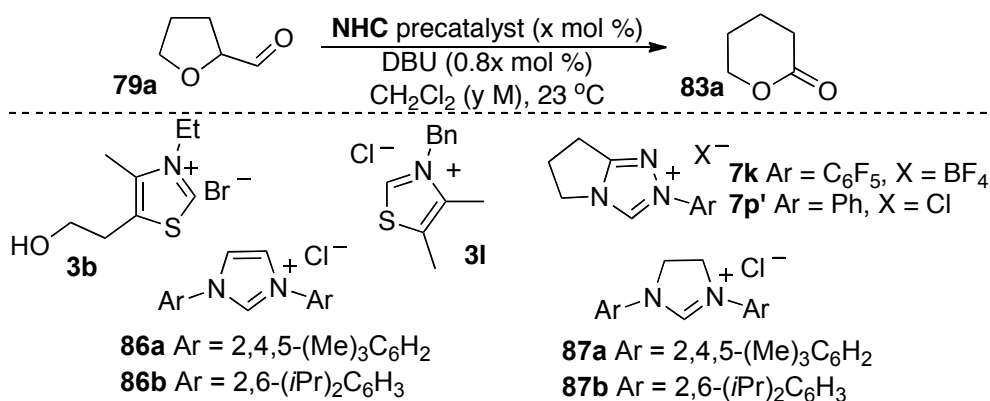
Scheme 4.3 Preparation of Oxetene Substrate **79m**.

4.1.3 Optimization of the Reaction

Various families of NHC precatalysts were screened for the ring expansion transformation (Table 4-1). Li Wang performed all of the optimization experiments with model tetrahydrofuran derivative **79a**. Thiazolium salts **3b** and **3l** were not ideal precatalysts for the transformation, furnishing the desired lactone in low yields and resulting in a complex mixture (entries 1-2). The yield obtained using **7k** was comparable to that obtained using thiazolium precatalyst **3l** (entry 3). In sharp contrast, the use of triazolium salt **7p'** resulted in the formation of only trace amounts of the lactone and the formation of many unidentified side products (entry 4). Exploring other families of carbene precursors, the use of imidazolium salts **86a** and **86b** resulted in no reaction (entries 5-6). Imidazolinium salt **87b**, in contrast to **87a**, led to the formation of the desired lactone **83a** in good yields (entries 7-8). The use of the imidazolinium salts bearing the same *N*-aryl substituents as the imidazolium salt counterparts clearly shows the importance of the heterocycle family for the ring expansion reaction (**86a** vs. **87a** and **86b** vs. **87b**). The reason behind the dramatic difference in reactivity between the two families of carbenes

is still unclear, but was presumably due to electronic factors. Gratifyingly, dropping the catalyst loading to 10 mol % and simultaneously increasing the concentration of the reaction led to the formation of the desired lactone in good yields (entry 9). Following the optimization of the reaction conditions for the ring expansion transformation, the scope of the reaction was investigated.

Table 4-1 Ring Expansion of Oxacycloalkane-2-carboxaldehydes: Reaction Optimization with Model Substrate **79a**.^a



entry	NHC precatalyst (x mol %)	concentration (M)	time (h)	yield (%) ^b
1	3b (50)	0.02	5	5
2	3l (50)	0.02	5	38
3	7k (50)	0.02	5	42
4	7p' (50)	0.02	5	0
5	86a (50)	0.02	5	0
6	86b (50)	0.02	4	0
7	87a (10)	0.5	17	35
8	87b (50)	0.02	5	82
9	85b (10)	0.5	13	78

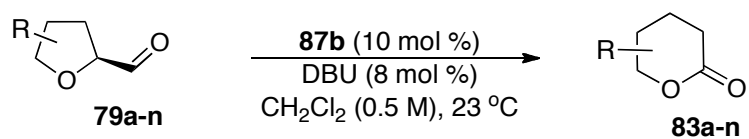
^a Unless otherwise noted, all reactions were performed by the addition of DBU to a solution of substrate **79a** (1 equiv.) and precatalyst in dichloromethane at 23 °C. ^b Yield of isolated pure product.

4.1.4 *Scope of the Reaction*

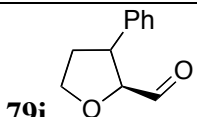
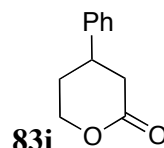
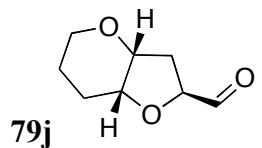
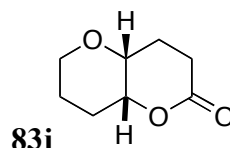
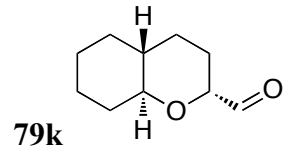
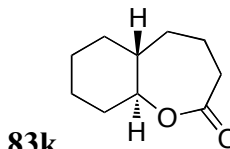
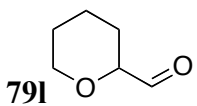
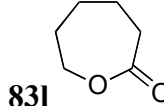
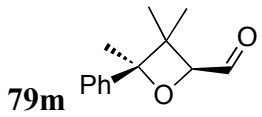
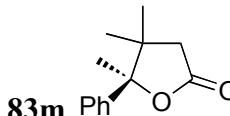
The scope of the reaction to access 5-, 6-, and 7-membered ring functionalized lactones was investigated (Table 4-2). The reaction was compatible with substrates **79b-d** bearing benzyloxymethyl and trialkylsilyloxymethyl groups (entries 2-4). However, isolation of the silyl protected lactone product **83c** proved to be difficult, despite the clean conversion to the desired lactone and the product was isolated in low yield (entry 3). Initially, the low yield was speculated to be a result of the labile *tert*-butyldimethylsilyl protecting group. However, the use of a triisopropylsilyl protecting group did not result in an improvement of the isolated yield (entry 4). Alkyl substituents at positions 3 and 4 of the substrate resulted in excellent yields (entries 5-6, 8-9). On the other hand, a phenyl substituent at the same positions resulted in no reaction or reduced reactivity and lower yields (entries 7,9). [6,6]-Bicyclic lactone **83j** could be also be accessed, albeit in lower yield, and after a longer reaction time (entry 10). Extension of the methodology to access [6,7]-bicyclic lactone **83k** proved to be more challenging (entry 11). Although no reaction was observed under the optimized condition, the desired lactone product was isolated in low yields, under high temperatures. Using higher temperature and extended reaction time, 7-membered lactone **83l** could also be obtained, albeit low yield (entry 12). Ring expansion of strained oxetane 2-carboxaldehyde efficiently furnished the γ -butyrolactone derivative **83m** in good yield (entry 13).

Table 4-2
Reaction.^a

Ring Expansion of Oxacycloalkane-2-carboxaldehydes: Scope of the



entry	substrate	time (h)	product	yield (%) ^b
1 ^c	79a	24	83a	78
2 ^{c,d}	79b	24	83b	98
	(1.3:1 dr)			
3	79c	24	83c	30
	(1.5:1 dr)			
4	79d	24	83d	32
	(1:1 dr)			
5 ^c	79e	24	83e	90
	(1.2:1 dr)			
6 ^c	79f	24	83f	94
	(1:1 dr)			
7	79g	24	83g	~38 ^e
	(1.3:1 dr)			
8	79h	24	83h	98
	(1.5:1 dr)			

9	 79i (1:1 dr)	48	 83i	0
10	 79j (>20:1 dr)	(4 d)	 83j	62
11 ^f	 79k (>20:1 dr)	(3 d)	 83k	~13 ^e
12 ^{c,g}	 79l	(10 d)	 83l	48
13 ^c	 79m (>20:1)	24	 83m	86

^a Unless otherwise noted, all reactions were performed by the addition of DBU (0.08 equiv.) to a solution of substrate **79** (1 equiv.) and precatalyst **87b** (0.10 equiv.) in dichloromethane (0.5 M). ^b Yield of isolated pure product. ^c Reaction performed by Li Wang. ^d >99% ee. ^e Product could not be isolated pure. ^f Reaction performed at 65 °C in a pressure vessel. ^g Reaction performed at 40 °C.

In contrast to the existing methodologies on the ring-opening of strained cyclic systems, an initial concern for the ring expansion methodology was the difficulty associated with the ring-opening of larger, non-strained ring systems (>5). Gratifyingly, the NHC-catalyzed ring expansion reaction of tetrahydrofuran derivatives occurred

efficiently at ambient temperature. Through computational studies,^{xi} the energy barrier associated with the ring-opening step of the transformation was found to be too high to proceed at room temperature (~50 kcal/mol). The high-energy barrier associated with the ring-opening step led to the consideration of the importance of the role of the base. In addition to generating the carbene species for the transformation, the conjugate acid of DBU was postulated to activate the substrate through hydrogen bonding interaction between the Breslow intermediate and the conjugate acid. Through the activation with DBU-H⁺, the barrier for the C-O cleavage was calculated to be ~13 kcal/mol. The activation of the substrate through a hydrogen bonding interaction could be useful for the extension of the methodology to rings featuring poor leaving groups. However, the possibility for the transformation to undergo activation via protonation or a different mechanistic pathway cannot be ruled out.

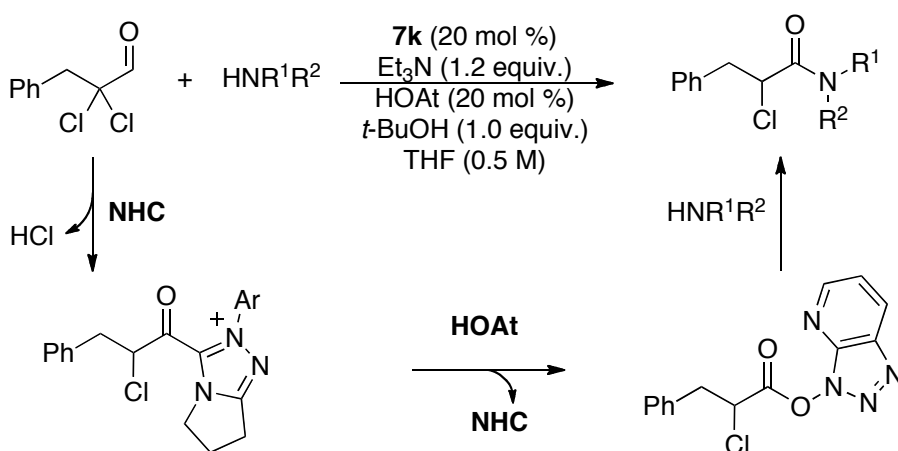
4.2 NHC-Catalyzed Ring Expansion of Prolinal Derivatives to Access Lactams

NHC-catalyzed internal redox transformations resulting in the formation of amide were initially reported through α -elimination and ring-opening processes by Rovis and Bode, respectively. A major challenge with the amidation of α -functionalized aldehydes is the intrinsic nature of the starting materials, aldehyde and amine nucleophile to undergo rapid formation of carbonyl imines.^{53c}

α,α -Dichlorinated aldehydes were shown by Rovis and coworkers to undergo slow NHC-catalyzed α -elimination in the presence of benzylamine (30% yield).⁵⁸

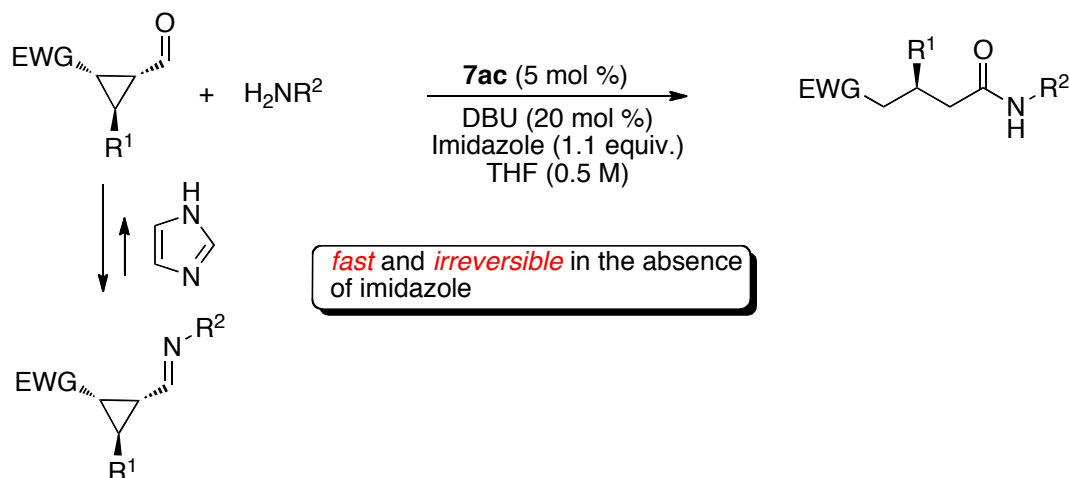
^{xi} Computational experiments were performed by Dr. Travis Dudding at Brock University. All calculations were made using the B3PW91/6-31G(d)//ONIOM(B3PW91/6-31G(d):uff) method.

However, significant improvement in the yield of the reaction (85-92% yield) was observed when a co-catalyst such as 1-hydroxybenzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt), (*N,N*-dimethylamino)pyridine (DMAP), imidazole, or pentafluorophenol (PFPOH) were employed. The coupling reagent HOAt proved to be the superior co-catalyst for the transformation. The proposed role of HOAt was to act as a nucleophilic relay catalyst by displacing the carbene and facilitating ring closure to the desired amide product (Scheme 4.4).



Scheme 4.4 Rovis' NHC-Catalyzed Redox Amidations of α -Functionalized Aldehydes with Amines.

Concurrently, the NHC-catalyzed ring-opening of cyclopropane derivatives to access amides was found to be completely hindered by the rapid formation of the corresponding imine. In contrast to Rovis' results, no reaction occurs in the absence of an additive and no improvement in the yield of the reaction was observed with the use of coupling agents.^{53c} However, the imine formation was suppressed in the presence of a stoichiometric amount of imidazole, leading to the formation of the amide in moderate to excellent yields.

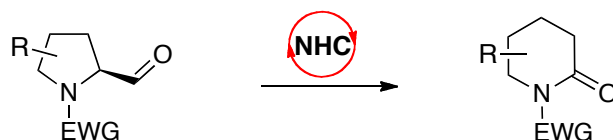


Scheme 4.5 Bode's NHC-Catalyzed Redox Amidations of α -Functionalized Aldehydes with Amines.

The ring expansion of strained β -lactam derivatives was reported by You and coworkers to occur efficiently in the absence of an additive and co-catalyst (Scheme 1.32, page 28). Presumably, the tethered secondary amide released during the catalytic cycle rapidly undergoes cyclization before any side reaction or inhibition can occur.

4.2.1 Research Objective

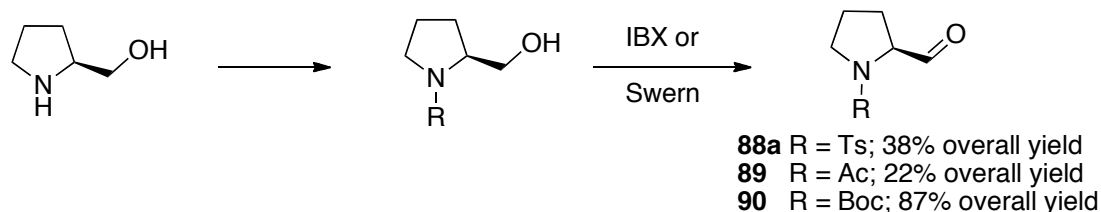
Following the NHC-catalyzed ring expansion reaction of oxacycloalkane-2-carboxaldehydes to furnish lactones, the extension of this methodology to the synthesis of lactams was explored. Nitrogen bearing electron-withdrawing group (EWG) proline derivatives were proposed to be ideal substrates for the transformation, as the EWG would activate the leaving group, facilitating the ring opening of these strained-free rings (Scheme 4.6). This methodology will give access to lactams, which serve as synthetically useful building blocks for the synthesis of natural products and biologically active compounds.⁸⁰



Scheme 4.6 Ring Expansion Reaction of Prolinal Derivatives Nitrogen-Bearing Electron-withdrawing Group.

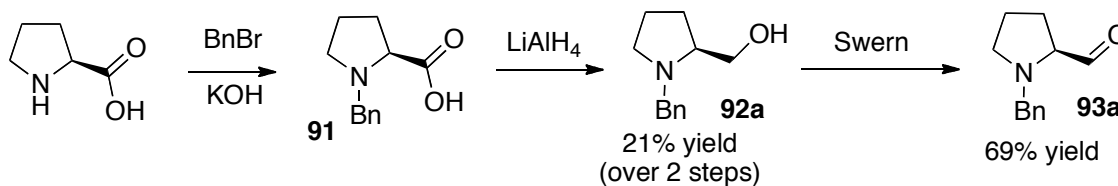
4.2.2 Synthesis of Starting Materials

In order to determine the scope of the NHC-catalyzed ring expansion, the substrates of interest were synthesized (Schemes 4.7 and 4.8). *N*-Ts, *N*-Ac, and *N*-Boc prolinal derivatives were synthesized from L-prolinol via *N*-functionalization of prolinol followed by oxidation with either IBX or Swern oxidation methods.^{81,82,83,84}



Scheme 4.7 Synthetic Route to *N*-Ts, *N*-Ac, and *N*-Boc Prolinal Substrates.

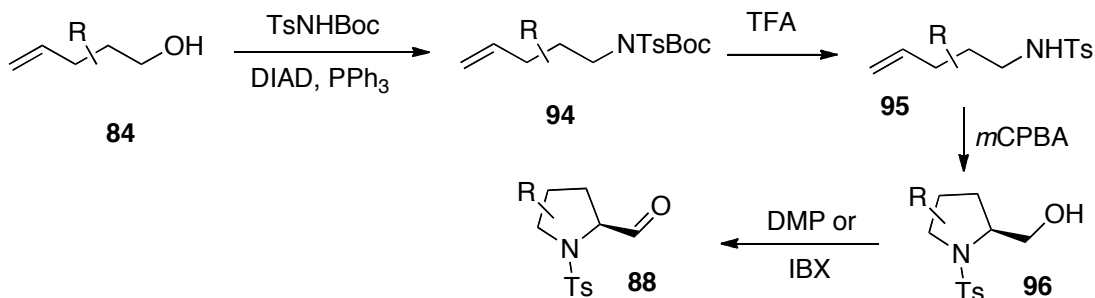
To test the electron-withdrawing group hypothesis, unactivated *N*-benzyl L-prolinal **93a** was synthesized from L-proline in three steps as shown in Scheme 4.8.



Scheme 4.8 Synthetic Route to *N*-Benzyl L-Prolinal.^{85,86,87}

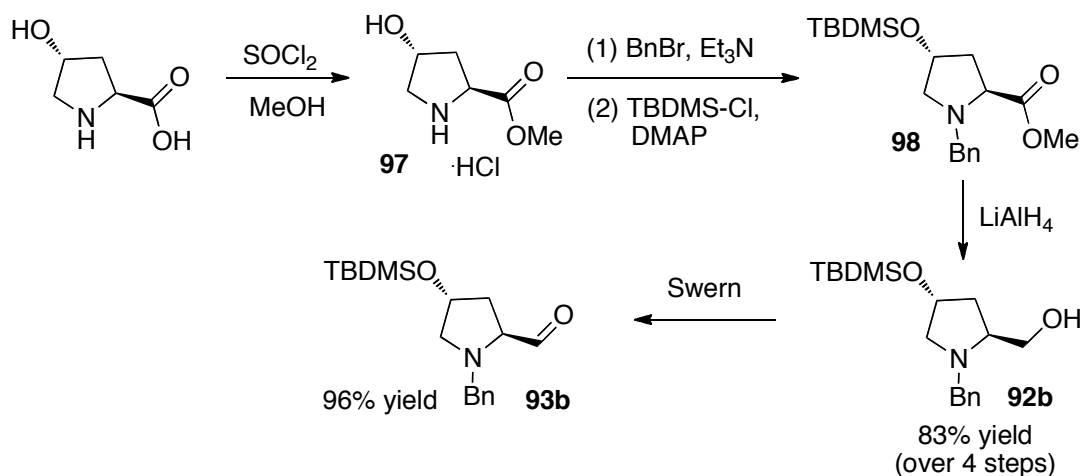
Functionalized *N*-Ts azacycloalkane-2-carboxaldehydes **88** were synthesized from the corresponding alcohol as shown as in Scheme 4.9. The *N*-Ts group was introduced via a Mitsunobu reaction and removal of the Boc activating group furnishes the acyclic

N-Ts **95**. Following a similar procedure to access functionalized tetrahydrofuran derivatives, the alkene moiety of **95** was epoxidized using *m*CPBA. Spontaneous epoxide opening by the pendant sulfonamide affords the desired prolinol derivative **96** which was then oxidized with IBX or Dess-Martin periodinane to furnish the aldehyde substrate **88**.



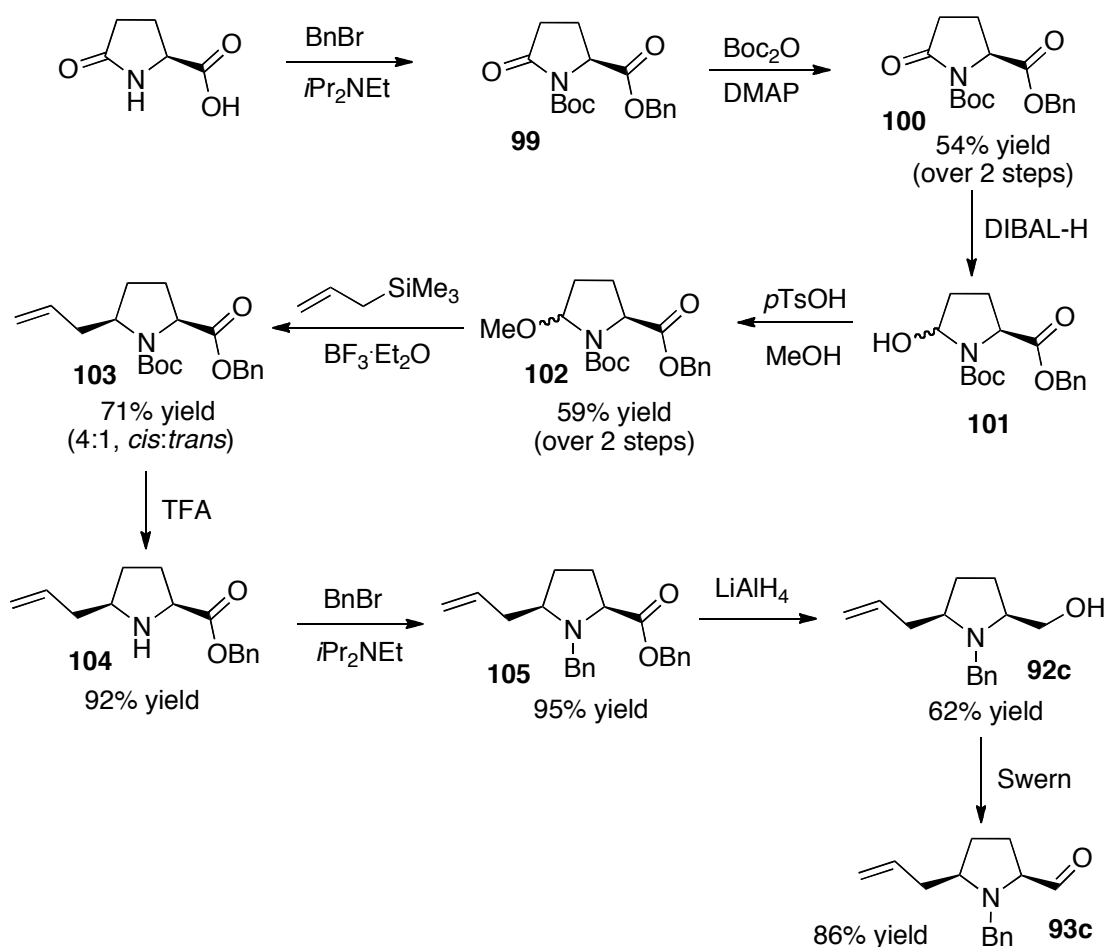
Scheme 4.9 General Method to Access Functionalized *N*-Tosyl Azacycloalkane-2-carboxaldehyde Substrates.

Unfortunately, the general method to synthesize *N*-tosyl substrates was not applicable to the synthesis of functionalized *N*-benzyl azacycloalkane-2-carboxaldehyde derivatives **93b-e**. The methyl ester salt **97** was synthesized from *trans*-4-hydroxy-L-proline (Scheme 4.10). *N*-Benzylation followed silyl protection of the alcohol, **98** was reduced with LiAlH_4 to furnish the prolinol **92b**.⁸⁸ Subsequently, the alcohol was oxidized to the aldehyde under Swern conditions to furnish the desired aldehyde substrate **93b**.



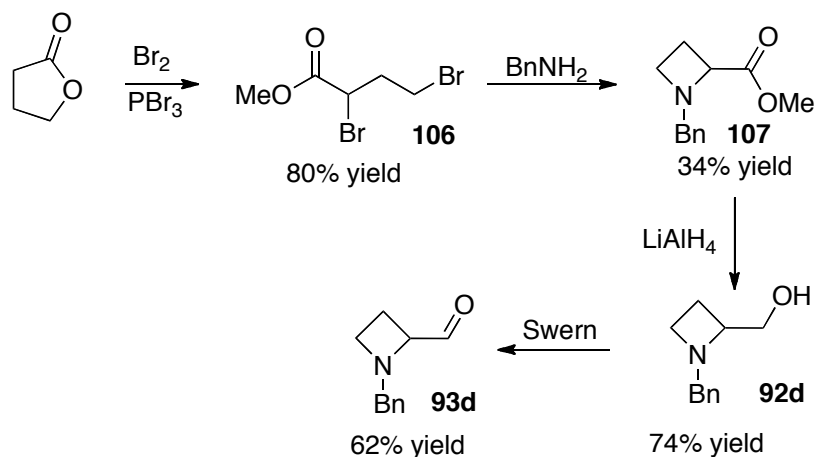
Scheme 4.10 Synthetic Pathway to Access (2*S*,4*R*)-1-Benzyl-4-(*tert*-butyl dimethylsilyloxy)pyrrolidine-2-carbaldehyde **93b**.⁸⁸

5-Allyl-1-benzylpyrrolidine-2-carbaldehyde **93c** was synthesized from L-pyroglutamic acid; intermediate **105** was synthesized following a sequence developed by the Aggarwal⁸⁹ and the Gloanec⁹⁰ groups (Scheme 4.11).



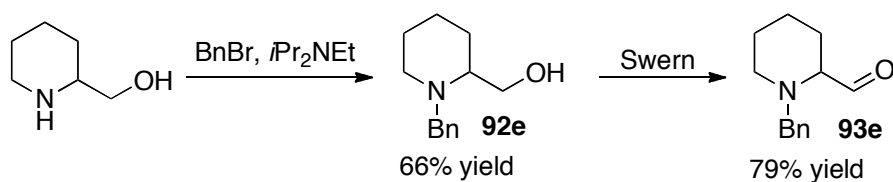
Scheme 4.11 Synthetic Pathway to Access (2*S*,5*R*)-5-Allyl-1-benzylpyrrolidine-2-carbaldehyde **93c**.

The *N*-benzyl azetidine substrate **93d** was synthesized from γ -butyrolactone, following Wasserman's procedure⁹¹ to obtain the dibromo methyl ester intermediate **106**. Subsequently, reaction with benzylamine furnishes the methyl ester azetidine **107**.⁹² The methyl ester was then reduced, followed by oxidation of the alcohol to furnish the desired aldehyde substrate **93d**.



Scheme 4.12 Synthetic Pathway to Access *N*-Benzylazetidine-2-carbaldehyde **91d**.

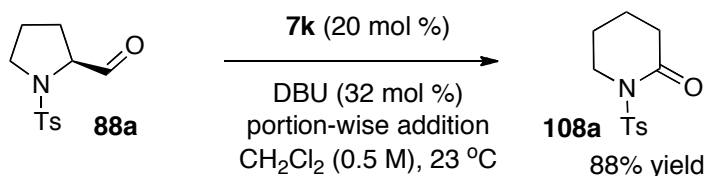
The synthesis of the 6-membered ring substrate **93e** was achieved in 2 steps from commercially available 2-piperidinemethanol (Scheme 4.13).



Scheme 4.13 Synthesis of 1-Benzylpiperidine-2-carbaldehyde.

4.2.3 Optimization of the Reaction

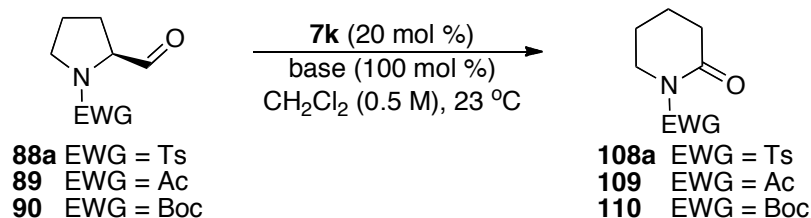
Although the preliminary optimized conditions determined by Li Wang⁹³ furnished the desired lactam in high yields, the reaction required portion-wise addition of DBU to generate the carbene to ensure continuing reaction progression (Scheme 4.14).



Scheme 4.14 Preliminary Optimized Reaction Conditions Established by Li Wang for the NHC-Catalyzed Ring Expansion Reaction.

A base screening was required as a result of the inconvenience of using DBU as the base for this reaction. Furthermore, it was found that DBU caused slow decomposition of the model substrate **88a** (Table 4-3, entry 1). Bases varying in strength were screened with the model substrate **88a** using 20 mol % catalytic loading of the triazolium salt **7k**. No reaction was observed when the strong base KHMDS was used to form the carbene catalyst (entry 2). Gratifyingly, weak bases such as *i*Pr₂NEt, Cs₂CO₃, and DMAP furnished the lactam product, *i*Pr₂NEt proved to be superior, whereas imidazole and pyridine did not result in any reaction (entries 3, 5-8). Excess base was used to determine the effect on the rate of the reaction. When 5 equivalents of *i*Pr₂NEt were employed, complete conversion of the aldehyde to the lactam was observed after 1 h (entry 4). Although the rate of the reaction increased with 5 equivalent of *i*Pr₂NEt only a marginal difference in the reaction time was observed in comparison to the use of 1 equivalent of *i*Pr₂NEt. The catalytic loading for the ring expansion reaction was investigated, using *i*Pr₂NEt as the ideal base. Dropping the catalytic loading to 10 mol % afforded complete conversion in 5 h, whereas the reaction stopped at 77% conversion after 30 h at 5 mol % catalytic loading (entries 9-10).

Table 4-3 Optimization of the Ring Expansion Lactamization Reaction: Base Screening.^a



entry	substrate	base (x mol %)	p <i>K</i> _a ^b	time (h)	conv. (%) ^c
1 ^d	88a	DBU (32)	16.6 (-)	24	>95
2 ^e	88a	KHMDS (16)	25.8 (-)	24	<5
3	88a	<i>i</i> Pr ₂ NEt (100)	12.5 (10.8)	2	>95
4	88a	<i>i</i> Pr ₂ NEt (500)	-	1	>95
5	88a	Cs ₂ CO ₃ (100)	- (10.3, 6.4)	5	>95
6	88a	DMAP (100)	11.2 (9.7)	4	80
7	88a	Imidazole (100)	- (7.0)	24	<5
8	88a	Pyridine (100)	5.5 (5.2)	24	<5
9 ^f	88a	<i>i</i> Pr ₂ NEt (100)		5	>95
10 ^g	88a	<i>i</i> Pr ₂ NEt (100)		30	77
11 ^f	89	<i>i</i> Pr ₂ NEt (100)		24	>95
12 ^f	90	<i>i</i> Pr ₂ NEt (100)		(7 d)	80

^a Unless otherwise noted, all reactions were performed by the addition of base to a solution of substrate (1 equiv.) and precatalyst **7k** (20 mol %) in dichloromethane (0.5 M) at 23 °C. ^b p*K*_a of the conjugate acid in THF;⁹⁴ values in H₂O⁹⁵ given in parentheses. ^c Conversion determined by ¹H NMR analysis of the crude reaction mixture. ^d Base was added portion-wise. ^e Catalyst was preformed by adding KHMDS (16 mol %) to the precatalyst **7k** (20 mol %) in dichloromethane (0.5 M), and then substrate **88a** (1 equiv.) was added. ^f 10 mol % **7k** was used. ^g 5 mol % **7k** was used.

With the optimized conditions on hand, *N*-Ts, *N*-Ac, and *N*-Boc L-prolinal substrates were subjected to the reaction conditions to compare their relative rate of reactivity (entries 9, 11-12). Sulfonamide **88a** and amide **89** furnished the lactam in

>95% conversion after 5 h and 24 h, respectively, whereas carbamate **90** gave 80% conversion to the desired lactam after 7 days. A trend can be established from the results obtained, where in the reaction tends to be faster with stronger electron-withdrawing groups. This observation was consistent with a rate-determining ring-opening step that would be accelerated with better leaving groups.

In contrast to strong or weak bases, bases with intermediate pK_a values (~ 10 in H_2O) were found to be remarkably efficient for the ring expansion transformation. Computational studies on the ring expansion of oxacycloalkanes suggested an important hydrogen bonding activation by the conjugate acid of DBU (vide supra). In line with this hypothesis, the observed importance of the pK_a value of the base suggests a dual role for the base in this transformation: (1) to generate the carbene catalyst and (2) to activate the sulfonamide-leaving group through hydrogen bonding via its conjugate acid (Figure 4.1).⁹⁶ Thus, the base required for efficient conversion needs to be strong enough to deprotonate the triazolium salt but weak enough for its conjugate acid to participate in hydrogen bonding catalysis.⁹⁷

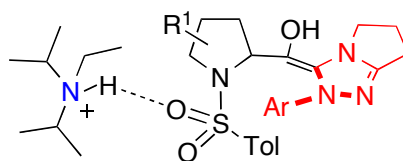


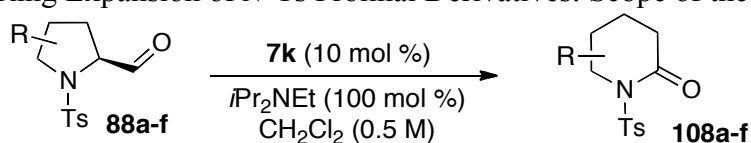
Figure 4.1 Proposed Hydrogen Bonding Interaction Between the Sulfonamide and the Conjugate Acid of iPr_2NEt .

4.2.4 Scope of the Reaction

The scope of the NHC-catalyzed ring expansion reaction was investigated for the synthesis of 4-, 5-, and 6-substituted lactams. The model substrate **88a** furnished the *N*-Ts

lactam **108a** in 90% yield (Table 4-4, entry 1). Longer reaction times were required with 3-substituted prolinal derivatives **88b-c**, presumably due to the increased steric hindrance (entries 2-4). Lactam **108b** was obtained in 81% yield at 10 mol % catalytic loading (entry 2). The reaction was repeated at 20 mol % catalytic loading, although complete conversion was observed after 5.5 h, no improvements in the yield of lactone **106b** was observed (entry 3). On the contrary, a larger alkyl substituent at the same position resulted in low yield of the lactam contaminated with traces of impurities (entry 4). In contrast to the ring expansion of oxacycloalkane-2-carboxaldehyde substrates bearing phenyl substituents, prolinal substrates bearing a phenyl ring were well tolerated (entries 5-6). Lactams bearing a phenyl substituent at position 5 or 6 were synthesized in 83% and 82% yields, respectively. Prolinal substrate **88f** with a 5-benzyloxymethyl substituent led to the formation of lactam **108f** in lower yield and the presence of numerous side products (entry 7). The reason behind the inefficient transformation of **88f** could be due to functional group incompatibility (vide infra).

The sluggish reaction rates of aldehydes **88b-c,f** were initially thought to be a result of the relative configuration of the substituents. The substituted prolinal substrates were synthesized as a mixture of diastereomers and the diastereomers may react at very different rates, thus resulting in an observed overall slow reaction. However, aliquots taken from the reaction mixture indicated that the reactivity of each diastereomer was similar.

Table 4-4 Ring Expansion of *N*-Ts Prolinal Derivatives: Scope of the Reaction.^a

entry	substrate	time (h)	product	yield (%) ^b
1	 88a	5	 108a	90
2	 88b	72	 108b	81
3 ^c	(2:1 dr)	5.5	108b	82
4	 88c (1.7:1 dr)	41	 108c	~38 ^d
5	 88d (1:1 dr)	2	 108d	83
6	 88e (1:1 dr)	24	 108e	82
7	 88f (2:1 dr)	24	 108f	49

^a Unless otherwise noted, all reactions were performed by the addition of *i*Pr₂NEt (1 equiv.) to a solution of substrate **88** (1 equiv.) and precatalyst **7k** (0.1 equiv.) in dichloromethane (0.5 M) at 23 °C. ^b Isolated yield. ^c Reaction was performed at 20 mol % cat. loading. ^d Product could not be isolated pure.

Intrigued by the postulated hydrogen bonding effect of the conjugate acid, the importance of the electron-withdrawing group was then examined. If the nitrogen-containing functional group was indeed activated through hydrogen bonding, simple amines should form stronger hydrogen bonds than sulfonamides, making them viable leaving groups. As a striking validation of this hypothesis, the reaction with *N*-benzyl prolinal **93a** rapidly furnished the desired lactam in 30 min. In comparison, *N*-Ts lactam **88a** required 5 h for complete conversion. In addition, *N*-benzyl lactam **111a** was obtained in quantitative yield following a simple filtration of the crude reaction mixture through a short pad of silica (Table 4-5, entry 1). To further investigate the dual role of the base, substrate **93a** was subjected to the same reaction conditions using DBU (8 mol %) instead of *i*Pr₂NEt (not shown). The observed reaction was significantly slower (<20% vs. >95% conversion after 30 min).^{xii} Intrigued by the efficiency of the transformation with *N*-benzyl prolinal, the scope of the reaction was investigated.

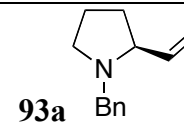
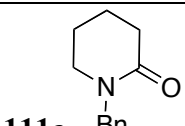
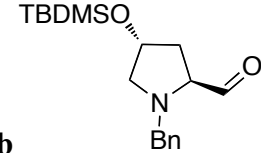
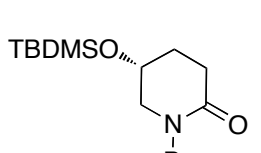
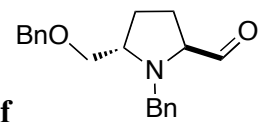
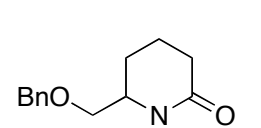
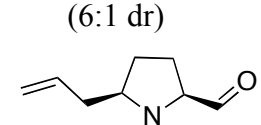
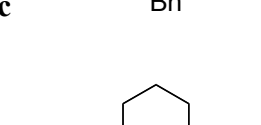
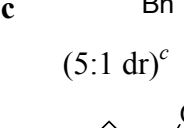
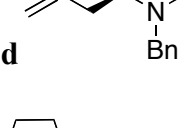
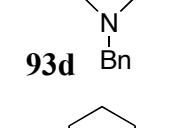
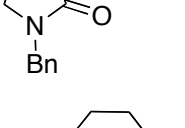
Functional groups such as silyl ethers were compatible with the reaction conditions, furnishing the desired lactam **93b** in 100% yield (entry 2).^{xiii} The presence of a 5-benzyloxymethyl substituent, such as in *N*-Ts prolinal **88f**, resulted in a sluggish reaction and the formation of numerous unidentified side products (entry 3). In contrast, the allyl substituent at the same position is well-tolerated, resulting in good yields (entry 4). Thus, benzyl ethers do not appear to be compatible with these reaction conditions, although the reason for this observation is not clear at this time. The reaction is not

^{xii} Slow decomposition of the aldehyde was observed in the presence of DBU; therefore, the stated conversion (formation of lactam product with respect to remaining aldehyde substrate) is an approximate value determined by ¹H NMR.

^{xiii} No purification was required, pure product was isolated through a simple filtration of the crude reaction mixture through a short pad silica.

limited to the synthesis of 6-membered lactams; *N*-benzyl 2-pyrrolidinone **111e** was synthesized from *N*-benzyl azetidine derivative **93d** in quantitative yield (entry 5).^{xiii} Of note, the reaction rate when using azetidine substrate **93d** was found to be similar to that using prolinal model substrate **93a** despite the increased strain in the former. The formation of 7-membered lactam **111f** proved to be more challenging; the reaction resulted in a complex mixture, with only trace amounts of the desired lactam (entry 6).

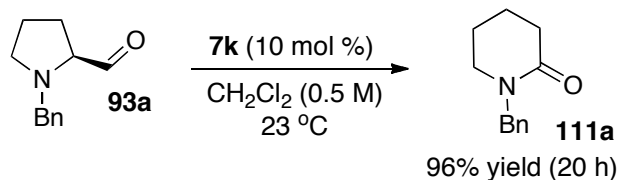
Table 4-5 Ring Expansion of *N*-Bn Prolinal Derivatives: Scope of the Reaction.^a

entry	substrate	time (h)	product	yield (%) ^b
1	 93a	0.5	 111a	100
2 ^c	 93b	(20 min)	 111b	100
3	 93f (6:1 dr)	24 h	 111c	49
4	 93c (5:1 dr) ^c	24 h	 111d	93
5	 93d	0.5	 111e	100
6	 93e	(4 d)	 111f	0

^a Unless otherwise noted, all reactions were performed by the addition of *i*Pr₂NEt (1 equiv.) to a solution of substrate **93** (1 equiv.) and precatalyst (0.1 equiv.) in dichloromethane (0.5 M) at 23 °C. ^b Yield of isolated pure product. ^c Reaction was performed with 20 mol % cat. loading of **7k**. ^c >99% ee.

In the case of *N*-Bn proline substrates, it was reasoned that the tertiary amine substrate could itself act as a base instead of *i*Pr₂NEt. To examine the efficiency of the transformation with the tertiary amine substrate as base, substrate **93a** was subjected to

the reaction conditions in the absence of *i*Pr₂NEt, and complete conversion was achieved after 20 h. Interestingly, the rate of the reaction suffered significantly in contrast to when the reaction was performed in the presence of an external base. At this point, it is unclear whether the basicity of the substrate (and thus the acidity of its conjugate acid) relative to that of *i*Pr₂NEt can alone explain the dramatic difference in reaction rates.



Scheme 4.15 NHC-Catalyzed Lactamization in the Absence of an External Base.

4.3 Conclusion

In summary, we have demonstrated NHC-catalyzed ring expansion reactions providing access to functionalized lactones,⁹⁸ *N*-Ts lactams and *N*-Bn lactams⁹⁹ in high yields. The ring expansion to access lactones was not limited to the synthesis of 6-membered ring systems, 5- and 7-membered ring lactones could also be accessed. On the other hand, the formation of lactams was restricted to 5- and 6-membered rings. Most notably and in contrast to the work of Bode and Rovis, both *N*-Ts and *N*-Bn lactams were accessible in the absence of a co-catalyst or additive. Also, enantiomerically-pure lactones **83b-d** and lactams **108f**, **111b-d** could be obtained from enantiomerically-pure starting materials.

Results from the computational experiments performed by our collaborator led to the extension of the reaction to unactivated *N*-alkyl prolinal substrates. The ring expansion of unactivated *N*-alkyl prolinal substrates in conjunction with the results obtained with the base screening highly suggest the importance of the dual role of the

base: (1) to generate the carbene catalyst through deprotonation and (2) to activate the substrates through hydrogen bonding via its corresponding conjugate acid.

CHAPTER 5: EXPERIMENTAL SECTION

5.1 General Methods

Anhydrous CH_2Cl_2 , diethyl ether, toluene, and THF were dried using a Braun Solvent Purification System and stored under nitrogen over 3 Å molecular sieves. Unless otherwise noted, all reactions were performed under an inert atmosphere of nitrogen.

Thin layer chromatography (TLC) was performed on Merck Silica Gel 60 F₂₅₄ and was visualized with UV light and 5% phosphomolybdic acid (PMA) or KMnO_4 . Silica gel 60 (40-63 mm) used for column chromatography was purchased from Silicycle Chemical Division. Purifications performed with CombiFlash Companion® was carried out by directly loading samples on prepacked silica gel Isco columns (Lincoln, NE). NMR spectra were measured in CDCl_3 solution at 500 MHz for ^1H and 125 MHz for ^{13}C . The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal standards for chemical shifts: CDCl_3 (7.26 ppm ^1H , 77.23 ppm ^{13}C); Acetone- d_6 (2.04 ppm ^1H , 29.8 ppm ^{13}C). The ^1H NMR chemical shifts and coupling constants were determined assuming first-order behavior. High-resolution mass spectra (HRMS) were obtained on a VG 70E double focusing high-resolution spectrometer. EI ionization was accomplished at 7 eV and CI at 50 eV with ammonia as the reagent gas. IR spectra were recorded on a Fourier transform interferometer using a diffuse reflectance cell (DRIFT); only diagnostic and/or intense peaks are reported. Unless otherwise stated, all samples were prepared on KBr film for IR analysis. Optical rotations were determined from an average of 5 measurements at ambient temperature using a 1 mL, 10 dm cell; the units are $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$, the concentrations are reported in units of g/100 mL. The

enantiomeric excess was determined, when necessary, using an HPLC system. CHIRALPAK® IA, IB, IC, and ASH columns were purchased from Daicel Chemical Industries, Ltd.

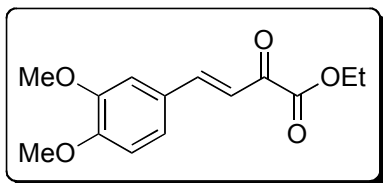
All commercially available aldehydes were purified by bulb-to-bulb distillation prior to use. Triazolium and thiazolium salts were prepared according to reported procedures. NHC precatalysts **7k** and **7ag** were prepared according to reported procedures^{100,101} and Eduardo Sánchez-Larios prepared triazolium precatalysts **7q**, **7u**, **7w**, **7ae**, and **7ai** according to reported procedures.^{63,102}

5.2 Experimental Procedures for the Highly Enantioselective Intermolecular Stetter Reaction

General Procedure for the Preparation of α -Ketoester Stetter Acceptors (43a-k)

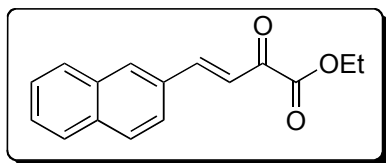
KOH (1.5 equiv.) in 50% MeOH:H₂O (4.4 M) was added dropwise to a solution of the appropriate aldehyde (1 equiv.) and sodium pyruvate (1 equiv.) in 50% MeOH:H₂O (1.5 M) at 0 °C, opened to the atmosphere. During the course of the addition, the reaction mixture turned yellow in color and precipitation occurred to form a thick slurry. The resulting reaction mixture was allowed to warm up to rt over 3-5 h. Aqueous HCl (1 M) was added and was extracted with ethyl acetate ($\times 3$). The combined organic extract was dried over Na₂SO₄, then concentrated under reduced pressure. The residueal oil was dissolved in ethanol (0.20 M, with respect to the aldehyde) and toluene (0.3 M, with respect to the aldehyde). Concentrated hydrochloric acid (0.8 equiv., 12.1 M) was added. The reaction mixture was heated to 95 °C for 4 h, then cooled to room temperature. The solvent was removed under reduced pressure. The crude product was purified by column chromatography to yield the desired product.

(E)-Ethyl 4-(3,4-dimethoxyphenyl)-2-oxobut-3-enoate (43f)



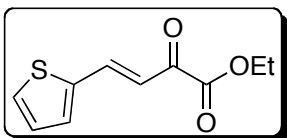
Yellow solid (55 mg, 4% yield; $R_f = 0.22$ (30% ethyl acetate in hexanes); **m.p.**: 59-61 °C; **FTIR** (KBr film) ν_{\max} (cm⁻¹): 2938, 2839, 1727, 1686, 1656, 1590, 1577, 1512, 1465, 1423, 1371, 1324, 1267, 1231, 1163, 1140, 1081, 1022, 984, 783; **¹H NMR** (500 MHz, CDCl₃) δ 7.83 (d, $J = 16.0$ Hz, 1H), 7.26-7.24 (m, 2H), 7.15 (d, $J = 1.8$ Hz, 1H), 6.90 (d, $J = 8.3$ Hz, 1H), 4.41 (q, $J = 7.1, 7.1$ Hz, 2H), 3.94 (s, 6H), 1.42 (t, $J = 7.1$ Hz, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 192.6, 187.0, 160.7, 152.0, 149.5, 148.8, 146.8, 130.0, 120.9, 118.7, 112.5, 111.7, 111.2, 62.8, 56.1, 56.0, 48.4, 43.1, 14.2; **HRMS** (EI⁺) m/z calculated for C₁₄H₁₆O₅ [M]⁺: 264.0998; found: 264.0999.

(E)-Ethyl 4-(naphthalen-2-yl)-2-oxobut-3-enoate (43g)



Yellow solid (977 mg, 71% yield). $R_f = 0.17$ (10% ethyl acetate in hexanes); **¹H NMR** (500 MHz, CDCl₃) δ 8.04 (d, $J = 17.0$ Hz, 1H), 8.06 (s, 1H), 7.90-7.85 (m, 3H), 7.77 (dd, $J = 8.8, 2.1$ Hz, 1H), 7.58-7.52 (m, 2H), 7.48 (d, $J = 16.4$ Hz, 1H), 4.42 (q, $J = 6.9, 6.9$ Hz, 2H), 1.44 (t, $J = 7.2$ Hz, 3H). Spectral data matched those previously reported.¹⁰³

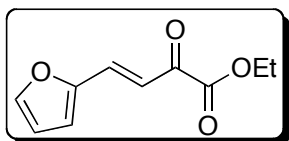
(E)-Ethyl 2-oxo-4-(thiophen-2-yl)but-3-enoate (43h)



Yellow solid (3.31 g, 74% yield). $R_f = 0.33$ (20% ethyl acetate in hexanes); **¹H NMR** (500 MHz, CDCl₃) δ 8.00 (d, $J = 15.8$ Hz, 1H), 7.52 (d, $J = 5.0$ Hz, 1H), 7.43 (d, $J = 3.5$ Hz, 1H), 7.16 (d, $J = 15.6$ Hz, 1H), 7.12

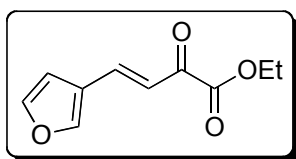
(dd, $J = 5.1, 3.9$ Hz, 1H), 4.39 (q, $J = 7.2, 7.2$ Hz, 2H), 1.41 (t, $J = 7.0$ Hz, 3H). Spectral data matched those previously reported.¹⁰⁴

(*E*)-Ethyl 4-(furan-2-yl)-2-oxobut-3-enoate (43i)



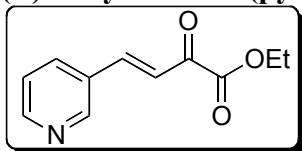
Yellow solid (831 mg, 35% yield). $R_f = 0.27$ (20% ethyl acetate in hexanes). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.62 (d, $J = 16.0$ Hz, 1H), 7.59-7.57 (m, 1H), 7.23 (d, $J = 15.6$ Hz, 1H), 6.82 (d, $J = 3.4$ Hz, 1H), 6.55-6.54 (m, 1H), 3.38 (q, $J = 7.1, 7.1$ Hz, 2H), 1.41 (t, $J = 7.1$ Hz, 3H). Spectral data matched those previously reported.¹⁰⁴

(*E*)-Ethyl 4-(furan-3-yl)-2-oxobut-3-enoate (43j)



Yellow solid (263 mg, 48% yield). $R_f = 0.31$ (20% ethyl acetate in hexanes); **m.p.**: 82-84 °C; **FTIR** (KBr film) ν_{max} (cm^{-1}): 3145, 3002, 1721, 1684, 1613, 1372, 1296, 1288, 1263, 1224, 1160, 1094, 1015, 991, 871, 827, 815, 787, 734, 594; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.80-7.76 (m, 2H), 7.46 (s, 1H), 7.05 (d, $J = 15.9$ Hz, 1H), 6.68 (s, 1H), 4.37 (q, $J = 7.1, 7.1$ Hz, 2H), 1.39 (t, $J = 7.1$ Hz, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 182.8, 162.4, 147.0, 145.1, 138.6, 123.3, 120.8, 107.6, 62.7, 14.3; **HRMS** (EI^+) m/z calculated for $\text{C}_{10}\text{H}_{10}\text{O}_4$ $[\text{M}]^+$: 194.0579; found: 194.0572.

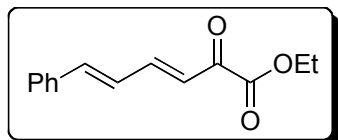
(*E*)-Ethyl 2-oxo-4-(pyridin-3-yl)but-3-enoate (43k)



Yellow solid (impure, ~60% purity). $R_f = 0.31$ (66% ethyl acetate in hexanes). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.83 (d, $J =$

1.7 Hz, 1H), 8.66 (dd, $J = 1.1, 4.6$ Hz, 1H), 7.97-7.94 (m, 1H), 7.85 (d, $J = 16.6$ Hz, 1H), 7.44 (d, $J = 16.0$ Hz, 1H), 7.37 (dd, $J = 8.0, 4.4$ Hz, 1H), 4.40 (q, $J = 7.1, 7.1$ Hz, 2H), 1.41 (t, $J = 7.1$ Hz, 3H). Spectral data matched those previously reported.¹⁰⁵

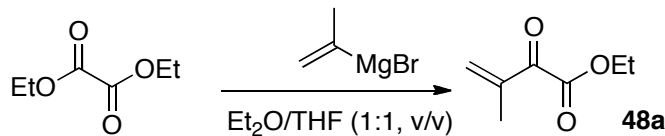
(3*E*,5*E*)-Ethyl 2-oxo-6-phenylhexa-3,5-dienoate (43l)



Yellow solid (677 mg, 46% yield). $R_f = 0.30$ (9% ethyl acetate in hexanes). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.65 (dd, $J = 15.3, 11.0$ Hz, 1H), 7.57-7.50 (m, 2H), 7.41-7.34 (m, 3H), 7.09 (d, $J = 1.5$ Hz, 1H), 7.01-6.96 (dd, 15.4, 11.0 Hz, 1H), 7.89 (d, $J = 15.3$ Hz, 1H), 4.35 (q, $J = 7.1, 7.1$ Hz, 2H), 1.40 (t, $J = 7.1, 7.1$ Hz, 3H). Spectral data matched those previously reported.¹⁰⁶

Procedure for the Synthesis of β -Alkyl Substituted β,γ -Unsaturated α -Ketoester

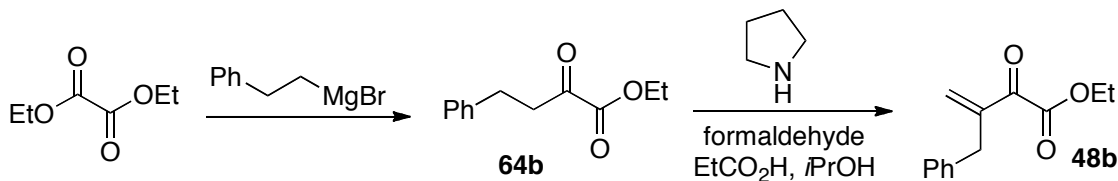
Ethyl 3-methyl-2-oxobut-3-enoate (48a)



Isopropenyl magnesium bromide (8.8 mL, 4.42 mmol, 0.5 M in THF) was added dropwise to a solution of diethyl oxalate (500 μL , 3.68 mmol) in anhydrous Et_2O /THF (7.0 M, 1:1 v/v) at -78°C , under inert atmosphere. The reaction mixture was stirred for 30 min, then quenched at -78°C with aqueous HCl (10 mL, 1.0 M), the resulting reaction mixture was warmed up to rt. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3×15 mL). The combined organic extracts was washed with brine (20 mL), dried over Na_2SO_4 , then concentrated under reduced pressure. The crude product was purified by bulb-to-bulb distillation at 70°C at 40 Torr to remove diethyl

oxalate, yielding the pure product as a light yellow oil (294 mg, 56% yield). ^1H NMR (500 MHz, CDCl_3) δ 6.18 (s, 1H), 6.10 (s, 1H), 4.36 (q, $J = 7.4, 7.4$ Hz, 2H), 1.94 (s, 3H), 1.37 (t, $J = 7.1, 7.1$ Hz, 3H). Spectral data matched those previously reported.¹⁰⁷

Ethyl 3-Benzyl-2-oxobut-3-enoate (**48b**)



Preparation of the Grignard reagent:

Powdered magnesium metal (190 mg, 7.7 mmol) was heated (~ 100 °C) under high vacuum for 10 min in a 3-neck round bottom flask, equipped with a condenser and a drop-funnel. The reaction vessel was then purged with nitrogen, the cycle was repeated a total of 3 times. The flask was allowed to cool down to rt, then anhydrous THF (2.0 mL) was added, followed by the dropwise addition of (2-bromoethyl)benzene (1.0 mL, 7.7 mmol) dissolved in anhydrous THF (3.0 mL) using the drop-funnel. The exothermic reaction was stirred for 1 h at rt.

*Synthesis of Substrate **64b**:*

In a separate round bottom flask, diethyl oxalate was dissolved in anhydrous THF (13 mL) and cooled to -78 °C. The freshly prepared Grignard reagent was then added dropwise to the round bottom flask -78 °C via syringe. After 1 h, the reaction was allowed to warm up to rt, HCl (10 mL, 1 M) was then added, followed by distilled water (10 mL), the organic layer was separated. The resulting aqueous layer was extracted with Et_2O (3×10 mL), the combined organic extract was washed with brine, dried over

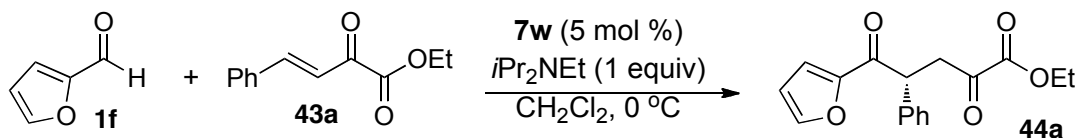
Na₂SO₄, and then concentrated under reduced pressure. The crude product was purified by column chromatography (10% ethyl acetate in hexanes, R_f = 0.28) to yield the product as a light yellow oil (900 mg, 59% yield). **¹H NMR** (500 MHz, CDCl₃) δ 7.31-7.28 (m, 2H), 7.22-7.20 (m, 3H), 4.31 (q, J = 7.1, 7.1 Hz, 2H), 3.18 (t, J = 7.2, 7.2 Hz, 2H), 2.96 (t, J = 7.4, 7.4 Hz, 2H), 1.36 (t, J = 7.3, 7.3 Hz, 3H). Spectral data matched those previously reported.¹⁰⁸

Propanoic acid (16 μ L, 0.220 mmol), followed by pyrrolidine (18 μ L, 0.220 mmol) was added to a solution of formaldehyde (180 μ L, 2.20, 37% w/w in H₂O) and α -ketoester **64b** (454 mg, 2.20 mmol) in *i*PrOH (220 μ L, 10 M). The reaction mixture was then heated to 45 °C for 1 h. The reaction was quenched with a saturated aqueous solution of NaHCO₃ (5 mL), then extracted with Et₂O (3 \times 5 mL), the combined organic extract was dried over Na₂SO₄, then concentrated under reduced pressure. The crude product was purified by column chromatography (20% ethyl acetate in hexanes, R_f = 0.52) to yield the product as a light yellow oil (119 mg, 25% yield). **FTIR** (KBr film) ν_{\max} (cm⁻¹): 3030, 2985, 1734, 1684, 1604, 1496, 1454, 1436, 1419, 1371, 1348, 1330, 1304, 1251, 1219, 1172, 1154, 1075; **¹H NMR** (500 MHz, CDCl₃) δ 7.32-7.30 (m, 2H), 7.26-7.22 (m, 1H), 7.20-7.18 (m, 2H), 6.23 (s, 1H), 5.98 (s, 1H), 4.35 (q, J = 6.9, 6.9 Hz, 2H), 3.65 (s, 2H), 1.36 (t, J = 7.4, 7.4 Hz, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 188.2, 164.0, 144.6, 137.8, 133.2, 129.4, 128.8, 126.8, 62.3, 35.9, 14.2; **HRMS** (EI⁺) m/z calculated for C₁₃H₁₄O₃ [M]⁺: 218.0943; found: 218.0948.

General procedure for the NHC-Catalyzed Intermolecular Stetter Reaction

Acceptor **43** (1 equiv.) and triazolium salt **7w** (0.05 equiv.) was added to an oven dried 5 mL Schlenk flask. The flask was then evacuated and purged with nitrogen. Anhydrous dichloromethane (0.20 M) was added and the mixture was then cooled to 0 °C for 5 min. Freshly distilled or prepared aldehyde **1** (1.5 equiv.) was added, followed by the slow addition of *i*Pr₂NEt (1 equiv.). The reaction was stirred at 0 °C until complete consumption of the starting material was observed by TLC. The reaction was quenched with AcOH (1 equiv.) and the resulting reaction mixture was filtered through a small pad of silica, washed with ethyl acetate (10 mL), and then concentrated under reduced pressure. The crude Stetter product was purified by flash column chromatography.

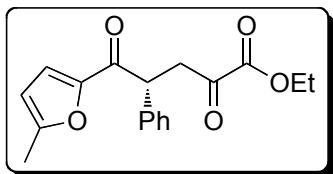
(+)-(R)-Ethyl 5-(furan-2-yl)-2,5-dioxo-4-phenylpentanoate (**44a**)



Acceptor **43a** (608 mg, 2.30 mmol) and precatalyst **7w** (49 mg, 0.12 mmol, 5 mol % cat. loading) dissolved in CH₂Cl₂ (15 mL, 0.20 M) were cooled to 0 °C, under N₂. Furfural (230 mL, 2.76 mmol) was added, followed by a slow addition of *i*Pr₂NEt (323 mL, 2.30 mmol) in CH₂Cl₂ (3.5 mL, final concentration of 0.15 M). The reaction was monitored by TLC; the reaction stopped progressing after 30 min. The reaction was quenched with AcOH (135 mL, 17.4 M, 2.30 mmol), the resulting reaction mixture was purified by FCC (25% ethyl acetate in hexanes, R_f = 0.30) to yield the desired product as a yellow oil (607 mg, 88% yield {93% b.r.s.m}, 89% ee). ¹H NMR (500 MHz, CDCl₃) δ 7.53 (s, 1H), 7.34-7.29 (m, 5H), 7.17 (d, *J* = 3.4 Hz, 1H), 6.47-6.45 (m, 1H), 4.93 (dd, *J* = 10.3, 4.2

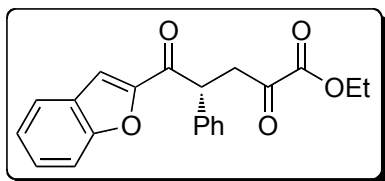
Hz, 1H), 4.32 (m, 2H), 3.96 (dd, $J = 19.3, 9.9$ Hz, 1H), 3.18 (dd, $J = 19.3, 4.8$ Hz, 1H), 1.36 (t, $J = 7.1, 7.1$ Hz, 3H). Spectral data matched those reported by Eduardo Sánchez-Larios.⁷³

(+)-(R)-Ethyl 5-(5-methylfuran-2-yl)-2,5-dioxo-4-phenylpentanoate (44b)



Orange oil (30 mg, 97% yield). $R_f = 0.17$ (20% ethyl acetate in hexanes); 83% ee; $[\alpha]_D^{25\text{ }^\circ\text{C}} = +145$ (c 2.6, CH_2Cl_2); HPLC analysis – Chiralcel IA column, 5% isopropanol in hexanes, 1.0 mL/min. Major: 25.5 min, minor: 20.5 min. **FTIR** (KBr film) ν_{max} (cm^{-1}): 2985, 2926, 1729, 1667, 1587, 1515, 1454, 1390, 1371, 1278, 1223, 1187, 1100, 1056, 1031, 903, 801, 732, 700, 570; **^1H NMR** (500 MHz, CDCl_3) δ 7.30-7.28 (m, 4H), 7.25-7.21 (m, 1H), 7.07 (d, $J = 3.5$ Hz, 1H), 6.07 (d, $J = 3.4$ Hz, 1H), 4.85 (dd, $J = 9.8, 4.3$ Hz, 1H), 4.30 (dddd, $J = 7.2, 7.2, 3.1$ Hz, 2H), 3.94 (dd, $J = 19.1, 9.9$ Hz, 1H), 3.14 (dd, $J = 19.1, 4.3$ Hz, 1H), 2.33 (s, 3H), 1.35 (t, $J = 7.1, 7.1$ Hz, 3H); **^{13}C NMR** (125 MHz, CDCl_3) δ 192.5, 186.1, 160.6, 158.3, 150.6, 138.3, 129.2, 128.4, 127.8, 120.8, 109.3, 62.7, 46.7, 43.0, 14.2, 14.2; **HRMS** (CI^+/NH_3) m/z calculated for $\text{C}_{18}\text{H}_{18}\text{O}_5$ $[\text{M}+1]^+$: 315.1232; found: 315.1223.

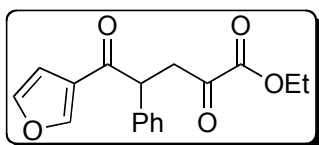
(R)-Ethyl 5-(benzofuran-2-yl)-2,5-dioxo-4-phenylpentanoate (44c)



Impure oil, ~90% purity. $R_f = 0.16$ (20% ethyl acetate in hexanes); 73% ee; HPLC analysis – Chiralcel IA column, 10% isopropanol in hexanes, 1.0 mL/min. Major: 21.9 min, minor: 20.0 min. **^1H NMR** (500 MHz, CDCl_3) δ 7.64 (d, $J = 7.8$ Hz, 1H), 7.53 (d, J

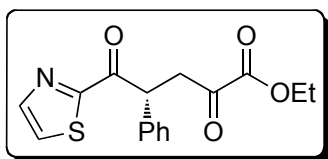
= 8.4 Hz, 1H), 7.50=7.48 (m, 1H), 7.46-7.41 (m, 2H), 7.39-7.37 (m, 2H), 7.33-7.30 (m, 2H), 7.28-7.23 (m, 1H), 5.07 (dd, $J = 10.1, 4.2$ Hz, 1H), 4.33 (dddd, $J = 7.1, 7.1, 7.1, 2.5$ Hz, 2H), 4.00 (dd, $J = 18.7, 9.7$ Hz, 1H), 3.23 (dd, $J = 19.3, 4.0$ Hz, 1H), 1.36 (t, $J = 7.1, 7.1$ Hz, 3H).

Ethyl 5-furan-3-yl)-2,5-dioxo-4-phenylpentanoate (44d)



The reaction was performed with 30 mol % catalytic loading at rt for 48 h. Colourless oil (10 mg, 31% yield). $R_f = 0.24$ (20% ethyl acetate in hexanes); 0% ee; HPLC analysis – Chiralcel IA column, 10% isopropanol in hexanes, 1.0 mL/min. Retention times = 12.9 min and 16.9 min. **FTIR** (KBr film) ν_{\max} (cm⁻¹): 2984, 1729, 1676, 1624, 1562, 1495, 1454, 1392, 1271, 1222, 1156, 1054, 903, 873, 733, 701, 599; **¹H NMR** (500 MHz, CDCl₃) δ 7.89 (s, 1H), 7.41-7.31 (m, 3H), 7.27-7.25 (m, 3H), 6.68 (d, $J = 1.2$ Hz, 1H), 4.70 (dd, $J = 9.8, 4.2$ Hz, 1H), 4.32 (dddd, $J = 5.8, 5.8, 5.8, 3.6$ Hz, 2H), 3.06 (dd, $J = 18.9, 9.9$ Hz, 1H), 3.06 (dd, $J = 18.9, 4.2$ Hz, 1H), 1.36 (t, $J = 7.1, 7.1$ Hz, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 192.8, 192.5, 160.7, 148.3, 144.0, 138.3, 129.5, 128.3, 128.0, 126.7, 109.3, 62.8, 51.7, 43.3, 14.2; **HRMS** (EI⁺) m/z calculated for C₁₇H₁₆O₅ [M]⁺: 300.0998; found: 300.0998.

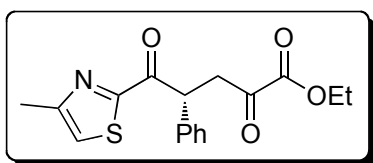
(+)-(R)-Ethyl 2,5-dioxo-4-phenyl-5-(thiazol-2-yl)pentanoate (44i)



Orange solid (28 mg, 74% yield). $R_f = 0.13$ (20% ethyl acetate in hexanes); 79% ee; $[\alpha]_D^{26} = +154$ (c 1.2, CH₂Cl₂); HPLC analysis – Chiralcel IA column, 10% isopropanol in hexanes, 1.0 mL/min. Major: 21.1 min and 13.3 min.); **m.p.**: 103-106 °C; **FTIR** (KBr

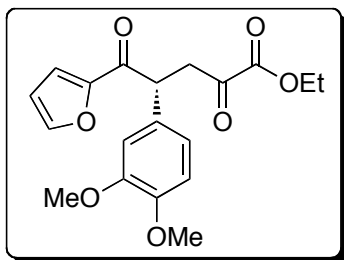
film) ν_{\max} (cm^{-1}): 2984, 1729, 1685, 1493, 1480, 1454, 1389, 1331, 1274, 1222, 1092, 1071, 1049, 911, 879, 854, 783, 752, 728, 698; ^1H NMR (500 MHz, CDCl_3) δ 7.98 (d, J = 3.0 Hz, 1H), 7.61 (d, J = 3.0 Hz, 1H), 7.42-7.41 (m, 2H), 7.31-7.28 (m, 2H), 7.24-7.21 (m, 1H), 5.53 (dd, J = 10.5, 4.0 Hz, 1H), 4.31 (dddd, J = 7.2, 7.2, 7.2, 1.3 Hz, 2H), 3.99 (dd, J = 19.4, 10.5 Hz, 1H), 3.34 (dd, J = 19.4, 4.0 Hz, 1H), 1.35 (t, J = 7.2, 7.2 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 192.3, 191.6, 166.0, 145.1, 136.7, 129.2, 128.9, 127.9, 126.7, 100.2, 62.8, 47.8, 43.4, 14.2; HRMS (EI^+) m/z calculated for $\text{C}_{16}\text{H}_{15}\text{NO}_4\text{S}$ $[\text{M}]^+$: 317.0722; found: 317.0719.

(+)-(R)-Ethyl 5-(4-methylthiazol-2-yl)-2,5-dioxo-4-phenylpentanoate (44j)



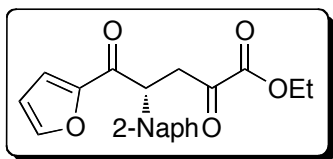
Light yellow oil (28 mg, 70% yield). R_f = 0.21 (20% ethyl acetate in hexanes); 75% ee; $[\alpha]_{\text{D}}^{26\text{ }^\circ\text{C}}$ = +86 (c = 1.0, CH_2Cl_2); HPLC analysis – Chiralcel IA column, 5% isopropanol in hexanes, 1.0 mL/min. Major: 13.6 min, minor: 12.5 min. FTIR (KBr film) ν_{\max} (cm^{-1}): 3105, 2983, 1729, 1683, 1506, 1494, 1432, 1391, 1374, 1274, 1222, 1092, 1070, 1049, 970, 899.1, 853, 756, 728, 698; ^1H NMR (500 MHz, CDCl_3) δ 7.43-7.41 (m, 2H), 7.31-7.26 (m, 2H), 7.24-7.21 (m, 1H), 7.17 (s, 1H), 5.50 (dd, J = 10.4, 3.8 Hz, 1H), 4.30 (q, J = 7.1, 7.1 Hz, 2H), 3.97 (dd, J = 19.4, 10.4 Hz, 1H), 3.34 (dd, J = 19.4, 4.1 Hz, 1H), 2.49 (s, 3H), 1.34 (t, J = 7.1, 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 192.3, 191.5, 164.8, 160.6, 155.6, 137.0, 129.1, 129.0, 127.8, 121.9, 62.8, 47.6, 43.4, 17.4, 14.2; HRMS (EI^+) m/z calculated for $\text{C}_{17}\text{H}_{17}\text{NO}_4\text{S}$ $[\text{M}]^+$: 331.0878; found: 331.0872.

(+)-(R)-Ethyl 4-(3,4-dimethoxyphenyl)-5-(furan-2-yl)-2,5-dioxopentanoate (44p)



Viscous yellow oil (24 mg, 86% yield). $R_f = 0.13$ (30% ethyl acetate in hexanes); 90% ee; $[\alpha]_D^{23} = +151$ ($c = 2.4$, CH_2Cl_2); HPLC analysis – Chiralcel IA column, 10% isopropanol in hexanes, 1.0 mL/min. Major: 25.1 min, minor: 18.6 min.; **FTIR** (KBr film) ν_{max} (cm^{-1}): 2938, 1729, 1672, 1592, 1568, 1517, 1466, 1420, 1394, 1263, 1143, 1097, 1081, 1053, 1027, 963, 900, 883, 766, 734; **^1H NMR** (500 MHz, CDCl_3) δ 7.53 (d, $J = 1.0$ Hz, 1H), 7.17 (d, $J = 3.3$ Hz, 1H), 6.87 (dd, $J = 8.2, 2.3$ Hz, 1H), 6.80-6.78 (m, 2H), 6.46 (dd, $J = 3.4, 1.7$ Hz, 1H), 4.86 (dd, $J = 9.7, 4.4$ Hz, 1H), 4.31 (dddd, $J = 7.3, 7.3, 3.0$ Hz, 2H), 3.92 (dd, $J = 18.9, 9.7$ Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.17 (dd, $J = 19.1, 4.4$ Hz, 1H), 1.35 (t, $J = 7.1, 7.1$ Hz, 3H); **^{13}C NMR** (125 MHz, CDCl_3) δ 192.6, 187.0, 160.7, 152.0, 149.5, 148.8, 146.8, 130.0, 120.9, 118.7, 112.5, 111.7, 111.2, 62.8, 56.1, 56.0, 48.4, 43.1, 14.2; **HRMS** (EI^+) m/z calculated for $\text{C}_{19}\text{H}_{20}\text{O}_7$ $[\text{M}]^+$: 360.1209; found: 360.1214.

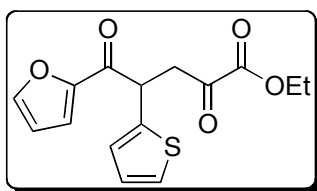
(+)-(R)-Ethyl 5-(furan-2-yl)-4-(naphthalen-2-yl)-2,5-dioxopentanoate (44q)



Off-white solid (30 mg, 97% yield). $R_f = 0.36$ (30% ethyl acetate in hexanes); 90% ee; $[\alpha]_D^{26} = +162$ ($c = 2.1$, CH_2Cl_2); HPLC analysis – Chiralcel IA column, 10% isopropanol in hexanes, 1.0 mL/min. Major: 25.1 min, minor: 18.6 min. **m.p.**: 110-112 °C; **FTIR** (KBr film) ν_{max} (cm^{-1}): 2983, 1729, 1673, 1568, 1508, 1466, 1508, 1466, 1394, 1273, 1226, 1163, 1097, 1081, 1052, 1016, 964, 900, 883, 821, 763, 479; **^1H NMR** (500 MHz, CDCl_3) δ 7.81-7.79 (m, 4H), 7.51-7.49 (m, 1H), 7.49-7.44 (m, 3H), 7.19 (d, $J = 3.6$

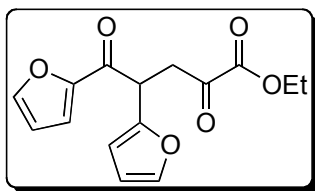
Hz, 1H), 6.43 (dd, $J = 3.6, 1.7$ Hz, 1H), 5.10 (dd, $J = 9.8, 4.3$ Hz, 1H), 4.31 (dddd, $J = 7.2, 7.2, 2.9$ Hz, 2H), 4.05 (dd, $J = 19.2, 9.9$ Hz, 1H), 3.26 (dd, $J = 19.2, 4.4$ Hz, 1H), 1.35 (t, $J = 7.1, 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 192.4, 186.8, 160.6, 152.0, 146.8, 135.2, 133.7, 132.9, 129.1, 128.0, 127.8, 127.5, 126.6, 126.4, 126.2, 118.8, 112.5, 62.8, 49.0, 43.1, 14.2; **HRMS** (EI^+) m/z calculated for $\text{C}_{21}\text{H}_{18}\text{O}_5$ $[\text{M}]^+$: 350.1154; found: 350.1151.

Ethyl 5-(furan-2-yl)-2,5-dioxo-4-(thiophen-2-yl)pentanoate (**44r**)



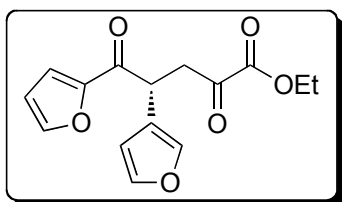
Yellow oil (24 mg, 80% yield). $R_f = 0.23$ (20% ethyl acetate in hexanes); 0% ee; HPLC analysis – Chiralcel IA column, 5% isopropanol in hexanes, 1.0 mL/min. Retention times = 24.3 min and 30.3 min; **FTIR** (KBr film) ν_{max} (cm^{-1}): 3134, 2983, 2923, 1729, 1674, 1568, 1466, 1393, 1260, 1195, 1163, 1094, 1081, 1050, 1016, 961, 900, 883, 767, 705; ^1H NMR (500 MHz, CDCl_3) δ 7.59 (d, $J = 1.0$ Hz, 1H), 7.26 (d, $J = 3.0$ Hz, 1H), 7.20 (dd, $J = 5.1, 0.9$ Hz, 1H), 6.97-6.96 (m, 1H), 6.94-6.92 (m, 1H), 6.52 (ddd, $J = 3.6, 1.6$ Hz, 1H), 5.22 (dd, $J = 10.0, 4.2$ Hz, 1H), 4.34 (dddd, $J = 10.9, 10.9, 2.1$ Hz, 2H), 3.99 (dd, $J = 19.2, 10.0$ Hz, 1H), 3.32 (dd, $J = 19.2, 4.2$ Hz, 1H), 1.38 (t, $J = 7.1, 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 192.0, 185.6, 151.6, 146.1, 139.5, 127.4, 126.4, 125.6, 119.0, 112.7, 62.9, 43.5, 43.1, 14.2; **HRMS** (EI^+) m/z calculated for $\text{C}_{15}\text{H}_{14}\text{O}_5\text{S}$ $[\text{M}]^+$: 306.0562; found: 306.0560.

Ethyl 4,5-di(furan-2-yl)-2,5-dioxopentanoate (44s)



Yellow oil (11 mg, 34% yield). R_f = 0.14 (20% ethyl acetate in hexanes); 0% ee; HPLC analysis – Chiralcel IA column, 5% isopropanol in hexanes, 1.0 mL/min. Retention times = 25.8 min and 30.2 min; **FTIR** (KBr film) ν_{\max} (cm^{-1}): 3136, 2985, 1730, 1678, 1568, 1502, 1466, 1394, 1256, 1162, 1098, 1082, 1070, 1052, 1014, 982, 962, 900, 883, 768; **^1H NMR** (500 MHz, CDCl_3) δ 7.59 (d, J = 1.0 Hz, 1H), 7.33 (d, J = 1.1 Hz, 1H), 7.25 (d, J = 4.8 Hz, 1H), 6.53 (dd, J = 3.6, 1.7 Hz, 1H), 6.29 (dd, J = 3.2, 1.9 Hz, 1H), 6.20 (d, J = 3.2 Hz, 1H), 5.05 (dd, J = 9.9, 4.3 Hz, 1H), 4.34 (dddd, J = 7.2, 7.2, 7.2, 1.9 Hz, 2H), 3.94 (dd, J = 19.1, 9.9 Hz, 1H), 3.28 (dd, J = 14.4, 4.3 Hz, 1H), 1.37 (t, J = 7.2, 7.2 Hz, 3H); **^{13}C NMR** (125 MHz, CDCl_3) δ 192.0, 184.2, 160.5, 151.7, 150.4, 147.2, 142.7, 119.1, 112.7, 111.0, 108.0, 62.9, 42.4, 40.1, 14.2; **HRMS** (EI^+) m/z calculated for $\text{C}_{15}\text{H}_{14}\text{O}_6$ $[\text{M}]^+$: 290.0790; found: 290.0787.

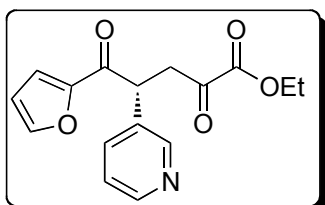
(+)-(R)-Ethyl 5-(furan-2-yl)-4-(furan-3-yl)-2,5-dioxopentanoate (44t)



Yellow oil (22 mg, 63% yield). R_f = 0.23 (30% ethyl acetate in hexanes); 88% ee; $[\alpha]_{\text{D}}^{22} = +88$ (c = 0.97, CH_2Cl_2); HPLC analysis – Chiralcel IA column, 5% isopropanol in hexanes, 1.0 mL/min. Major: 28.0 min, minor: 24.8 min.; **FTIR** (KBr film) ν_{\max} (cm^{-1}): 3136, 2985, 1729, 1675, 1568, 1466, 1395, 1258, 1157, 1097, 1082, 1053, 1022, 964, 901, 883, 873, 855, 767, 602; **^1H NMR** (500 MHz, CDCl_3) δ 7.57 (d, J = 0.7 Hz, 1H), 7.47 (s, 1H), 7.33 (s, 1H), 7.23 (d, J = 3.6 Hz, 1H), 6.51 (dd, J = 3.4, 1.5 Hz, 1H), 6.63 (s, 1H), 4.87 (dd, J = 9.6, 4.6 Hz, 1H), 4.31 (dddd, J = 7.4, 7.4, 1.5 Hz, 2H), 3.82 (dd, J =

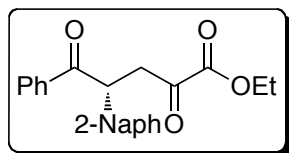
19.2, 9.6 Hz, 1H), 3.20 (dd, $J = 19.2, 4.6$ Hz, 1H), 1.35 (t, $J = 7.1, 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 192.3, 186.8, 160.6, 151.8, 146.9, 143.7, 140.4, 121.8, 118.6, 112.7, 110.0, 62.8, 42.0, 39.0, 14.2; HRMS (EI^+) m/z calculated for $\text{C}_{15}\text{H}_{14}\text{O}_6$ $[\text{M}+1]^+$: 290.0790; found: 290.0792.

(*R*)-Ethyl 5-(furan-2-yl)-2,5-dioxo-4-(pyridin-3-yl)pentanoate (44u)



Impure yellow oil, ~80% purity. $R_f = 0.17$ (66% ethyl acetate in hexanes); 77% ee; HPLC analysis – Chiralcel IB column, 20% isopropanol in hexanes, 1.0 mL/min. Major: 23.2 min, minor: 26.4 min; ^1H NMR (500 MHz, CDCl_3) δ 8.66 (d, $J = 2.1$ Hz, 1H), 8.51 (dd, $J = 5.0, 1.7$ Hz, 1H), 7.65-7.63 (m, 1H), 7.55 (d, $J = 1.0$ Hz, 1H), 7.23 (d, $J = 3.6$ Hz, 2H), 6.50 (dd, $J = 3.6, 1.5$ Hz, 1H), 4.98 (dd, $J = 9.5, 4.4$ Hz, 1H), 4.32 (dddd, $J = 7.1, 7.1, 7.1, 2.0$ Hz, 2H), 3.96 (dd, $J = 19.3, 9.7$ Hz, 1H), 3.12 (dd, $J = 19.3, 4.6$ Hz, 1H), 1.36 (t, $J = 7.4, 7.4$ Hz, 3H).

(+)-(*R*)-Ethyl 4-(naphthalene-2-yl)-2,5-dioxo-5-phenylpentanoate (44aa)

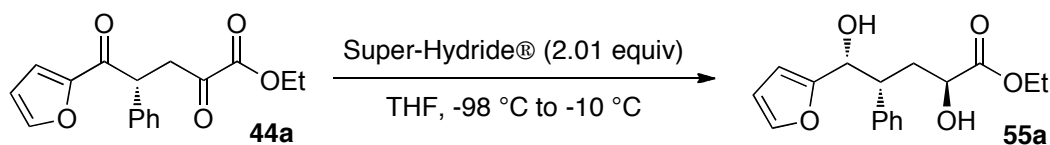


A mixture of α -ketoester acceptor **43g** (30 mg, 0.12 mmol), $\text{Mg}(\text{OtBu})_2$ (2.0 mg, 0.012 mmol) and triazolium salt **7w** (5.0 mg, 0.0120 mmol) was purged with nitrogen for 30 min. Anhydrous CH_2Cl_2 (590 μL , 0.2 M) was added, followed by freshly distilled benzaldehyde (18 μL , 0.18 mmol). The resulting suspension was cooled to 0 $^\circ\text{C}$ for 5 min, then $i\text{Pr}_2\text{NEt}$ (22 μL , 0.12 mmol) was added and the reaction mixture was stirred at 0 $^\circ\text{C}$. The reaction was quenched with AcOH (7.0 μL , 0.12 mmol). The reaction mixture was then filtered through a small pad

of silica and washed with EtOAc (10 mL), the filtrate was then concentrated and purified by Combiflash (gradient eluent: 100% hexanes to 10% ethyl acetate in hexanes) to yield the pure Stetter adduct as a white solid (10 mg, 24% yield). $R_f = 0.20$ (10% ethyl acetate in hexanes); 91% ee; $[\alpha]_D^{22} = +186$ ($c = 0.59$, CH_2Cl_2); HPLC analysis – ChiralPak AD column, 10% isopropanol in hexanes, 1.0 mL/min. Major: 21.2 min, minor: 15.0 min; **m.p.**: 102-105 °C; **FTIR** (KBr film) ν_{max} (cm^{-1}): 1728, 1681, 1596, 1581, 1507, 1448, 1388, 1369, 1255, 1222; **^1H NMR** (500 MHz, CDCl_3) δ 7.99-7.97 (m, 2H), 7.81-7.75 (m, 3H), 7.23 (d, $J = 2.0$ Hz, 1H), 7.48-7.43 (m, 3H), 7.41 (dd, $J = 8.2, 2.4$ Hz, 1H), 7.37-7.33 (m, 2H), 5.29 (dd, $J = 9.8, 4.3$ Hz, 1H), 4.32 (dddd, $J = 7.1, 7.1, 7.1, 2.0$ Hz, 2H), 4.07 (dd, $J = 19.2, 9.4$ Hz, 1H), 3.23 (dd, $J = 19.2, 4.3$ Hz, 1H), 1.36 (t, $J = 7.4, 7.4$ Hz, 3H); **^{13}C NMR** (125 MHz, CDCl_3) δ 198.2, 192.7, 160.7, 136.1, 135.7, 133.8, 133.3, 132.8, 129.5, 129.2, 128.7, 128.0, 127.9, 127.4, 126.7, 126.4, 126.0, 62.8, 49.3, 44.2, 14.2; **HRMS** (EI^+) m/z calculated for $\text{C}_{23}\text{H}_{20}\text{O}_4$ $[\text{M}]^+$: 360.1362; found: 360.1368.

Procedures for the Synthetic Application of the Stetter Adducts to Access Diverse Building Blocks (55, 59, 60,61,64-66)

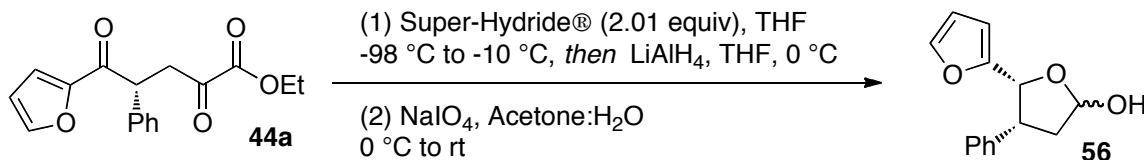
(*R*)-Ethyl 5-(furan-2-yl)-2,5-dihydroxy-4-phenylpentanoate (52a)



Super-hydride (380 mL, 0.38 mmol, 1.0 M in THF) was added dropwise to the substrate **44a** (57 mg, 0.19 mmol) in THF (1.9 mL, 0.10 M) at -98 °C, under inert atmosphere. The reaction was allowed to slowly warm up to -10 °C over 2 h. The reaction was quenched

with distilled water (50 mL), followed by the addition of 2 M HCl (0.5 mL), then neutralized with sat. NaHCO₃ (aq), the resulting aqueous solution was extracted with ethyl acetate (3x), the combined organic extracts were dried over Na₂SO₄, then concentrated under reduced pressure. The diol was purified by FCC (30% ethyl acetate in hexanes, R_f = 0.15 and 0.12) as a colorless oil (46 mg, 80% yield, 4:1 dr). **FTIR** (KBr film) ν_{max} (cm⁻¹): 3446, 3030, 2925, 1729, 1603, 1496, 1454, 1384, 1369, 1264, 1213, 1146, 1105, 1082, 1011, 923, 884, 742, 702, 599; **¹H NMR** (500 MHz, CDCl₃) δ 7.39-7.34 (m, 4H, both diast.), 7.30-7.25 (m, 6H, both diast.), 7.21-7.18 (m, 2H, both diast.), 6.32-6.31 (m, 1H, major diast.), 6.21 (d, J = 3.10 Hz, 1H, major diast.), 6.20-6.19 (m, 1H, minor diast.), 6.03 (d, J = 3.1 Hz, 1H, minor diast.), 4.85 (d, J = 7.5 Hz, 1H, major diast.), 4.82 (d, J = 7.2 Hz, 1H, minor diast.), 4.20-4.10 (m, m, 4H, both diast.), 3.83 (dd, J = 15.0, 6.88 Hz, 1H, minor diast.), 3.75 (d, J = 10.5 Hz, 1H, major diast.), 3.54-3.47 (m, 2H, both diast.), 2.86-2.82 (br s, 1H), 2.70-2.66 (br s, 1H, major diast.), 2.48-2.45 (br s, 1H, minor diast.), 2.30-2.15 (m, 2H, minor diast.), 2.18-2.12 (m, 1H, major diast.), 2.05-2.01 (br s, 1H, major diast.), 1.71 (dddd, J = 14.4, 11.1, 3.8 Hz, 1H, major diast.), 1.28-1.23 (m, 6H, both diast.); **Major diastereomer:** **¹³C NMR** (125 MHz, CDCl₃) δ 175.4, 154.8, 142.3, 139.5, 129.1, 129.0, 127.6, 110.4, 107.8, 71.9, 68.5, 61.9, 47.9, 37.1, 14.3; **Minor diastereomer:** **¹³C NMR** (125 MHz, CHCl₃) δ 175.5, 155.2, 141.8, 140.6, 128.7, 128.7, 127.1, 110.2, 107.1, 72.3, 68.6, 61.9, 47.6, 36.2, 14.4; **HRMS** (EI⁺) m/z calculated for C₁₇H₂₀O₅ [M]⁺: 304.1310; found: 304.1309.

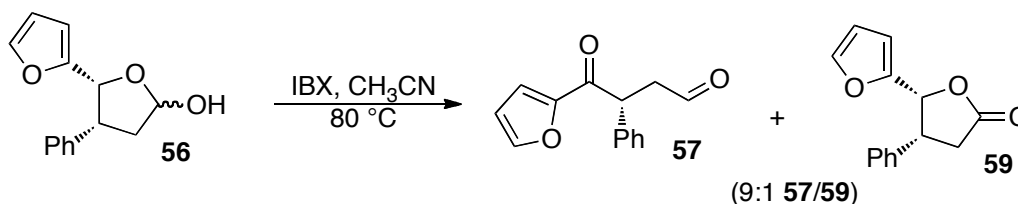
(4*R*,5*R*)-5-(Furan-2-yl)-4-phenyl-tetrahydrofuran-2-ol (56)



Super-Hydride® (1.5 mL, 1.50 mmol) was slowly added to Stetter adduct **44a** (100 mg, 0.33 mmol, 90% ee) in anhydrous THF (3.3 mL, 0.10 M) at -98 °C, under inert atmosphere. The reaction was slowly warmed up to 0 °C over 30 min. A solution of LiAlH₄ in THF (330 µL, 1.0 M) was added to the reaction mixture at 0 °C, then slowly warmed up to rt over 30 min. The reaction was quenched with distilled water (2 mL), 15% aqueous NaOH was added (1.5 mL), followed by the addition MgSO₄ then stirred for 1 h. The solids were filtered off and washed with EtOAc (10 mL), the filtrate was collected and concentrated under reduced pressure. The crude product was then dissolved in acetone:H₂O (3.3 mL, 2.5:1 v/v) then cooled to 0 °C. NaIO₄ (140 mg, 0.67 mmol) was then added, stirred for 30 min then slowly warmed up to rt over 1 h. Distilled water (10 mL) was then added, the aqueous solution was extracted with EtOAc (3 × 10 mL), the combined organic extracts was dried over Na₂SO₄, then concentrated under reduced pressure. The crude product was purified by flash column chromatography (30% ethyl acetate in hexanes, *R_f* = 0.24) to yield the pure product as a colorless oil (34 mg, 44% yield). **FTIR** (KBr film) ν_{max} (cm⁻¹): 3408, 3029, 2949, 1723, 1603, 1498, 1455, 1149, 1010, 739, 699; **¹H NMR** (500 MHz, CHCl₃) δ 7.31-7.27 (m, 1H), 7.19-7.12 (m, 3H), 7.00 (d, *J* = 6.7 Hz, 2H), 5.93 (d, *J* = 4.9 Hz, 1H), 5.91 (d, *J* = 3.0 Hz, 1H), 5.50 (d, *J* = 7.8 Hz, 1H), 4.06 (ddd, *J* = 10.2, 10.2, 7.4 Hz, 1H), 2.65 (ddd, *J* = 12.7, 12.7, 5.2 Hz, 1H), 2.32 (dd, *J* = 12.8, 7.3 Hz, 1H); **¹³C NMR** (125 MHz, CHCl₃) δ 152.6, 141.9, 138.3,

128.2, 128.1, 126.7, 110.0, 108.1, 98.5, 78.4, 46.7, 38.6; **HRMS** (EI^+) m/z calculated for $\text{C}_{14}\text{H}_{14}\text{O}_3$ $[\text{M}]^+$: 230.0942; found: 230.0941.

(+)-(R)-4-(Furan-2-yl)-4-oxo-3-phenylbutanal (57**)**

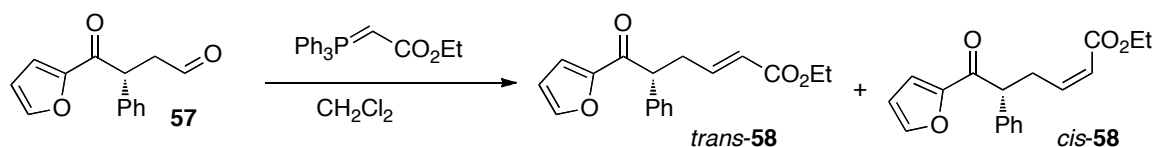


IBX (51 mg, 0.18 mmol) was added to lactol **56** (21 mg, 0.091 mmol) in acetonitrile (300 μL , 0.30 M), the suspension was then refluxed at 80 $^{\circ}\text{C}$ for 2 h. The resulting reaction mixture was cooled to rt then filtered through a small pad of silica and Celite® and washed with EtOAc (10 mL), the filtrate was collected then the solvent was removed. The crude product was purified by column chromatography (2% ethyl acetate in toluene) to yield the aldehyde product **57** as a colorless oil (15 mg, 71% yield, R_f = 0.20) and lactone **59** as a colorless oil (4 mg, 19% yield, R_f = 0.14). Aldehyde **57**: $[\alpha]_{\text{D}}^{24\text{ }^{\circ}\text{C}}$ = +25 (c = 0.92, CH_2Cl_2); **FTIR** (KBr film) ν_{max} (cm^{-1}): 2923, 1720, 1673, 1567, 1466, 1393, 1016, 759, 701; **^1H NMR** (500 MHz, CHCl_3) δ 9.79 (s, 1H), 7.53 (s, 1H), 7.53 (d, J = 1.1 Hz, 1H), 7.32-7.30 (m, 4H), 7.25-7.22 (m, 1H), 7.18 (d, J = 4.0 Hz, 1H), 6.46 (dd, J = 3.5, 1.7 Hz, 1H), 4.93 (dd, J = 9.9, 4.2 Hz, 1H), 3.60 (dd, J = 18.7, 9.5, Hz, 1H), 3.18 (dd, J = 19.2, 4.2 Hz, 1H), 2.84 (dd, J = 18.9, 4.2 Hz, 1H); **^{13}C NMR** (125 MHz, CHCl_3) δ 199.9, 187.1, 152.1, 147.0, 138.0, 129.3, 128.4, 127.8, 118.6, 112.5, 47.7, 47.4; **HRMS** (EI^+) m/z calculated for $\text{C}_{14}\text{H}_{14}\text{O}_3$ $[\text{M}]^+$: 230.0942; found: 230.0941. Lactone **59**: **^1H NMR** (500 MHz, CHCl_3) 7.26-7.24 (m, 1H), 7.22-7.19 (m, 2H), 7.02 -7.00 (m, 2H), 6.15 (dd, J = 3.2, 1.9 Hz, 1H), 6.05 (d, J = 3.2 Hz, 1H), 5.73 (d, J = 7.8 Hz, 1H), 4.13 (ddd, J

= 11.4, 8.3, 8.3 Hz, 1H), 3.28 (dd, J = 17.1, 11.4 Hz, 1H), 2.90 (dd, J = 17.1, 8.3 Hz, 1H).

Spectral matched those reported by Eduardo Sánchez-Larios.⁷³

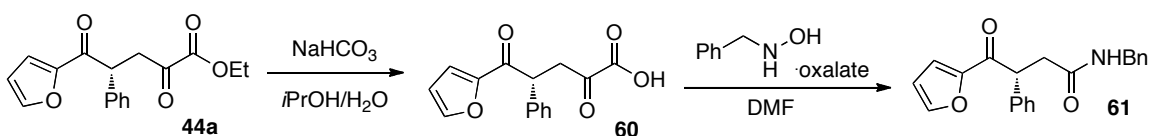
(+)-(R,E)-Ethyl 6-(furan-2-yl)-6-oxo-5-phenylhex-2-enoate (*trans*-58 and *cis*-58)



Ethyl (triphenylphosphoranylidene)acetate (21 mg, 0.059 mmol) was added to aldehyde **57** (9.0 mg, 0.0394 mmol) in anhydrous CH_2Cl_2 (400 μL , 0.1 mL) at rt, under inert atmosphere. The reaction mixture was stirred at rt for 21 h, then the solvent was removed, the crude product was purified by column chromatography (10 % ethyl acetate in hexanes, *cis*-isomer: R_f = 0.21, *trans*-isomer: R_f = 0.11) to yield the *cis*-**58** as colorless oil (1 mg) and the *trans*-**58** as a colorless oil (9 mg) (combined yield = 83%). *trans*-isomer: 10% ee; $[\alpha]_D^{22} = +24$ (c = 0.61, CH_2Cl_2); HPLC analysis – Chiracel IC column, 10% isopropanol in hexanes, 1.0 mL/min. Major: 26.2 min, minor: 24.4 min; **FTIR** (KBr film) ν_{max} (cm^{-1}): 1717, 1673, 1567, 1466, 1392, 1271, 1161, 1033, 764, 700; **^1H NMR** (500 MHz, CHCl_3) 7.53 (d, J = 1.0 Hz, 1H), 7.33-7.29 (m, 4H), 7.25-7.22 (m, 1H), 7.16 (d, J = 3.5 Hz, 1H), 6.85 (ddd, J = 14.5, 7.2, 7.2 Hz), 6.46 (dd, J = 3.5, 1.6 Hz, 1H), 5.83 (d, J = 15.6 Hz, 1H), 4.49 (dd, J = 7.4, 7.4 Hz, 1H), 4.13 (q, J = 7.1, 7.1 Hz, 2H), 3.09 (ddd, J = 16.2, 8.3, 8.3 Hz, 1H), 2.69 (ddd, J = 15.2, 7.0, 7.9 Hz, 1H), 1.24 (t, J = 7.1, 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, CDCl_3) δ 187.5, 166.5, 152.3, 146.8, 145.8, 138.2, 129.2, 128.4, 127.8, 123.6, 118.4, 112.6, 60.4, 52.9, 35.5, 14.4; **HRMS** (EI^+) m/z calculated for $\text{C}_{18}\text{H}_{18}\text{O}_4$ $[\text{M}]^+$: 298.1205; found: 298.1203.

cis-isomer: ^1H NMR (500 MHz, CHCl_3) 7.52 (d, $J = 1.0$ Hz, 1H), 7.36 -7.34 (m, 3H), 7.32-7.29 (m, 2H), 7.16 (d, $J = 3.6$ Hz, 1H), 6.45 (dd, $J = 3.4, 1.5$ Hz, 1H), 6.16 (ddd, $J = 11.8, 7.6, 7.6$ Hz, 1H), 5.77 (ddd, $J = 3.2, 1.5, 1.5$ Hz, 1H), 4.54 (dd, $J = 7.6, 7.6$ Hz, 1H), 4.17 (q, $J = 7.3, 7.3$ Hz, 2H), 3.36 (ddd, $J = 15.1, 7.8, 7.8$ Hz, 1H), 3.24 (ddd, $J = 14.5, 7.8, 7.8$ Hz, 1H), 1.27 (t, $J = 6.9, 6.9$ Hz, 3H).

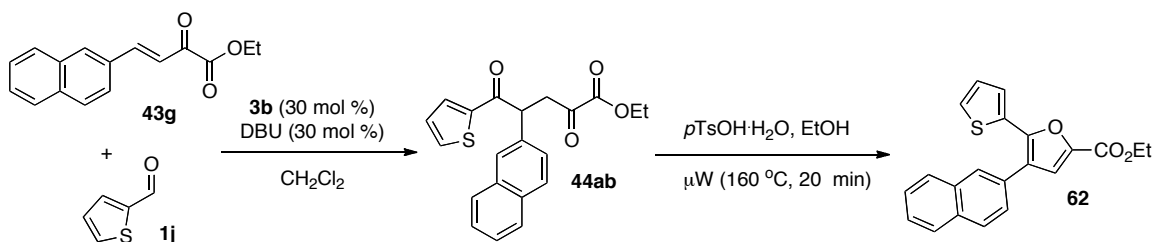
(*R*)-*N*-Benzyl-4-(furan-2-yl)-4-oxo-3-phenylbutanamide (61)



NaHCO_3 (10 mg, 0.12 mmol) was added to α -ketoester **44a** (12 mg, 0.41 mmol, 80% ee) 50% $i\text{PrOH}$ in water (200 μL). The resulting reaction mixture was heated to 50 $^\circ\text{C}$ for 20 min. $i\text{PrOH}$ was removed under reduced pressure and the resulting aqueous solution was extracted with Et_2O (3×5 mL), the combined organic extracts was dried over Na_2SO_4 , then concentrated under reduced pressure. The crude α -ketoacid was dissolved in anhydrous DMF (410 μL , 0.10 M), under nitrogen, followed by the addition of *N*-benzylhydroxylamine¹⁰⁹ (14 mg, 0.062 mmol). The resulting reaction mixture was heated to 50 $^\circ\text{C}$ for 24 h. The reaction was allow to cool to rt, then CH_2Cl_2 (3 mL) was added, followed by HCl (5 mL, 1 M), the organic layer was then separated and the resulting aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic extracts was washed with brine (15 mL), dried over Na_2SO_4 , then the solvent was removed in vacuo. The crude amide product was purified by column chromatography (50% ethyl acetate in hexanes, $R_f = 0.28$) to yield the impure product as an impure dark purple oil (5 mg, ~80% purity). 60% ee; HPLC analysis – Chiracel IA column, 30%

isopropanol in hexanes, 1.0 mL/min. Major: 9.4 min, minor: 8.2 min; $^1\text{H NMR}$ (500 MHz, CDCl_3) 8.45 (br s, 1H), 7.53 (d, $J = 1.0$ Hz, 1H), 7.32-7.30 (m, 9H), 7.27-7.23 (m, 1H), 7.16 (dd, $J = 3.6, 0.6$ Hz, 1H), 6.46 (dd, $J = 3.6, 1.7$ Hz, 1H), 4.93 (dd, $J = 10.1, 4.4$ Hz, 1H), 4.01 (dd, $J = 19.3, 10.1$ Hz, 1H), 3.22 (dd, $J = 18.9, 4.6$ Hz, 1H).

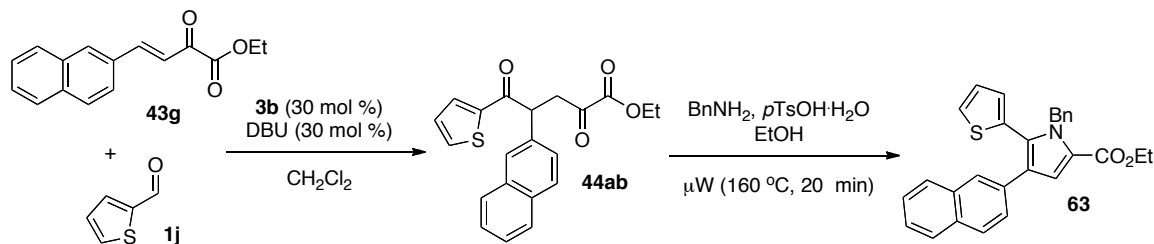
Ethyl 4-(naphthalen-2-yl)-5-(thiophen-2-yl)furan-2-carboxylate (**62**)



α -Ketoester acceptor **43g** (51 mg, 0.201 mmol) and triazolium salt **3b** (15 mg, 0.060 mmol) was purged with nitrogen for 30 min. Anhydrous CH_2Cl_2 (1.0 mL, 0.2 M) was added, followed by the addition of 2-thiophenecarboxaldehyde (28 μL , 0.301 mmol) and DBU (9 μL , 0.060 mmol), the resulting reaction mixture was stirred at rt over 19 h. The reaction was quenched with AcOH (20 μL) then filtered through a small pad of silica, and then washed with EtOAc (10 mL), the filtrate was then concentrated. The crude product was purified by Combiflash (gradient eluent: 10% ethyl acetate in hexanes to 20% ethyl acetate in hexanes) to yield the product as a bright yellow oil (44 mg, 60% yield). $R_f = 0.29$ (20% ethyl acetate in hexanes); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.82-7.79 (m, 3H), 7.74 (dd, $J = 3.5, 0.8$ Hz, 1H), 7.55 (dd, $J = 4.7, 0.8$ Hz, 1H), 7.50-7.42 (m, 4H), 7.01 (dd, $J = 4.7, 2.8$ Hz, 1H), 5.12 (dd, $J = 10.8, 4.3$ Hz, 1H), 4.32 (dddd, $J = 7.0, 7.0, 7.0, 2.0$ Hz, 2H), 4.05 (dd, $J = 18.8, 9.8$ Hz, 1H), 3.23 (dd, $J = 19.1, 4.3$ Hz, 1H), 1.35 (t, $J = 7.1, 7.1$ Hz, 3H).

p-Toluenesulfonic acid monohydrate (20 mg, 0.104 mmol) was added to α -ketoester adduct **44ab** (19 mg, 0.052 mmol) in EtOH (520 μ L, 0.1 M). The resulting reaction mixture was heated in the microwave reactor at 160 $^{\circ}$ C for 20 min. The reaction was diluted with EtOAc (5 mL), followed by the addition of distilled water (5 mL). The organic layer was separated and the resulting aqueous layer was extracted with EtOAc (3 \times 5 mL). The combined organic extracts were dried over MgSO₄ then concentrated under reduced pressure. The desired furan was purified by Combiflash (gradient eluent: 100% hexanes to 6% ethyl acetate in hexanes) to yield the product as a colourless oil (10 mg, 55% yield). R_f = 0.30 (6% ethyl acetate in hexanes); **FTIR** (KBr film) ν_{\max} (cm⁻¹): 2982, 1721, 1543, 1513, 1499, 1468, 1411, 1393, 1369, 1354, 1316, 1271, 1250, 1212, 1187, 1160, 1126, 1107, 1017; **¹H NMR** (500 MHz, CDCl₃) δ 7.85 (s, 1H), 7.80-7.77 (m, 3H), 7.75-7.72 (m, 1H), 7.45-7.41 (m, 3H), 7.26-7.25 (m, 2H), 7.18-7.16 (m, 2H), 6.87 (dd, J = 5.1, 3.5 Hz, 1H), 4.32 (q, J = 7.4, 7.4 Hz, 2H), 1.32 (t, J = 7.0, 7.0 Hz, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 158.9, 148.4, 143.0, 133.6, 133.1, 131.9, 129.9, 128.7, 128.2, 128.0, 127.6, 126.9, 126.9, 126.8, 126.7, 126.6, 123.9, 121.6, 61.3, 14.6; **HRMS** (EI⁺) m/z calculated for C₁₈H₁₈O₄ [M]⁺: 348.0820; found: 348.0808.

Ethyl 1-benzyl-4-(naphthalene-2-yl)-5-(thiophen-2-yl)-1*H*-pyrrole-2-carboxylate (**63**)

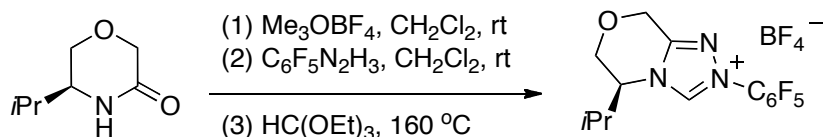


Stetter adduct **44ab** was synthesized as described for the synthesis of furan derivative **63**. *p*-Toluenesulfonic acid monohydrate (21 mg, 0.109 mmol) was added to Stetter adduct

44ab (20 mg, 0.055 mmol) and benzylamine (18 μ L, 0.164 mmol) in EtOH (270 μ L, 0.2 M), followed by the addition of a small spatula tip of MgSO₄. The resulting reaction mixture was heated in the microwave reactor at 160 °C for 20 min. The reaction was diluted with EtOAc (5 mL), followed by the addition of distilled water (5 mL). The organic layer was separated and the resulting aqueous layer was extracted with EtOAc (3 \times 5 mL). The combined organic extracts was dried over MgSO₄ then concentrated under reduced pressure. The desired pyrrole **63** was purified by Combiflash (gradient eluent: 100% hexanes to 10% ethyl acetate in hexanes) to yield the product as a yellow solid (9 mg, 38% yield). R_f = 0.38 (10% ethyl acetate in hexanes). **m.p.**: 135-137 °C; **FTIR** (KBr film) ν_{max} (cm⁻¹): 2980, 1704, 1602, 1531, 1496, 1480, 1464, 1446, 1427, 1405, 1387, 1342, 1300, 1259, 1237, 1215, 1174, 1087, 1075; **¹H NMR** (500 MHz, CDCl₃) 7.69-7.67 (m, 1H), 7.64-7.59 (m, 3H), 7.35 (s, 1H), 7.34-7.29 (m, 2H), 7.26 (dd, J = 8.6, 2.0 Hz, 1H), 7.21-7.17 (m, 3H), 7.15-7.11 (m, 1H), 6.92 (dd, J = 5.1, 3.5 Hz, 1H), 6.86 (d, J = 7.0 Hz, 2H), 6.84 (dd, J = 3.5, 1.2 Hz, 1H), 5.55 (s, 2H), 4.19 (q, J = 7.4, 7.4 Hz, 2H), 1.24 (t, J = 7.0, 7.0 Hz, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 161.1, 139.3, 133.7, 132.6, 132.2, 131.8, 130.8, 130.2, 128.7, 128.6, 128.1, 127.8, 127.7, 127.5, 127.1, 126.6, 126.4, 126.1, 126.0, 125.9, 125.6, 123.8, 117.8, 60.4, 49.4, 14.6; **HRMS** (EI⁺) m/z calculated for C₂₈H₂₃NO₂S [M]⁺: 437.1450; found: 437.1453.

5.3 Experimental Procedures for the Highly Enantioselective Intermolecular Cross-Benzoin Reaction

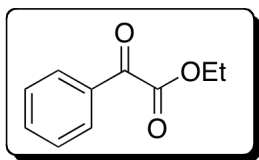
(+)-(S)-5-Isopropyl-2-(perfluorophenyl)-6,8-dihydro-5H-[1,24]triazoleo [3,4-c]oxazin-2-ium tetrafluoroborate (7ah)



Trimethyloxonium tetrafluoroborate (826 mg, 5.58 mmol, 1 equiv.) was added to a stirring solution of (S)-5-isopropylmorpholin-3-one¹¹⁰ (799 mg, 5.58 mmol, 1 equiv.) in anhydrous dichloromethane (28 mL, 0.20 M), under inert atmosphere. The reaction was allowed to stir until the solution turned clear and homogenous (t = 8 h). Pentafluorophenyl hydrazine (1.11 g, 5.58 mmol, 1 equiv.) was then added and the resulting reaction mixture was stirred for 15 h. The solvent was then removed *in vacuo* then the remaining residue was placed to dry under high vacuum (~0.5 Torr) for 1 h. Chlorobenzene (28 mL, 0.20 M) was then added, followed by triethylorthoformate (8.40 mL, 50.2 mmol, 9 equiv.), the resulting reaction mixture was heated to reflux at 130 °C, opened to the air for 24 h. An additional portion of triethylorthoformate (8.4 mL, 50.2 mmol, 9 equiv.) was added and stirred at 130 °C for 24 h. The reaction was then allowed to cool to room temperature then concentrated under reduced pressure. The crude product was purified by flash column chromatography (100% ethyl acetate, R_f = 0.10), the isolated product was then triturated with toluene to yield the product as a white solid (558 mg, 24% yield). **m.p.**: 103-104 °C; $[\alpha]_D^{23}$ °C = +24 (c 1.5, acetone); **FTIR** (KBr pellet) ν_{\max} (cm⁻¹): 3130, 3100, 2979, 1594, 1553, 1531, 1517, 1474, 1399, 1241, 1216,

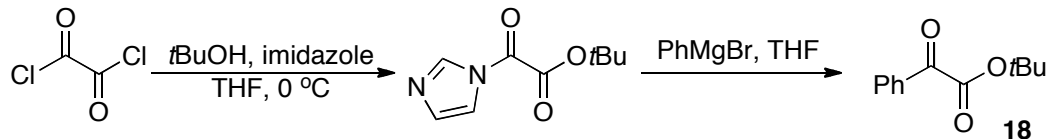
1124, 1116, 1077, 1063, 1040, 1009, 988, 855, 743; **¹H NMR** (500 MHz, Acetone – d₆) δ 10.52 (s, 1H), 5.39 (d, *J* = 16.6 Hz, 1H), 5.21 (d, *J* = 16.6 Hz, 1H), 4.89-4.82 (m, 1H), 4.45 (dd, *J* = 12.8, 3.0 Hz, 1H), 3.31 (dd, *J* = 13.0, 3.8 Hz, 1H), 2.63-2.52 (m, 1H), 1.18 (d, *J* = 6.9 Hz, 3H), 1.10 (d, *J* = 6.9 Hz, 3H); **¹³C NMR** (125 MHz, Acetone – d₆) – δ 64.6, 62.9, 62.5, 31.7, 19.1, 17.9; **HRMS** (ESI⁺) *m/z* calculated for C₁₄H₁₃N₃OF₅ [M]⁺: 334.0973 found: 334.0984.

Ethyl 2-oxo-2-phenylacetate (64a)¹¹¹



Phenyl magnesium bromide solution (8.8 mL, 8.84 mmol, 1.2 equiv., 1.0 M in THF) was added dropwise to a solution of diethyl oxalate (1.0 mL, 7.36 mmol, 1 equiv.) in anhydrous diethyl ether (25 mL, 0.3 M) at -78 °C, under inert atmosphere. The resulting solution was warmed up to 10 °C over 2 h, then quenched with a saturated aqueous solution of NH₄Cl (10 mL). The organic extract was separated, and the resulting aqueous fraction was extracted with diethyl ether (2 × 10 mL). The combined organic extracts were dried over Na₂SO₄, then concentrated under reduced pressure. The crude product was purified by bulb-to-bulb distillation (130 °C at 1.2 Torr) to yield the product as a light yellow oil (965 mg, 74% yield). **¹H NMR** (500 MHz, CDCl₃) δ 8.01 (d, *J* = 7.1 Hz, 2H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 2H), 4.45 (q, *J* = 7.0 Hz, 2H), 1.43 (t, *J* = 7.0 Hz, 3H). Spectral data matched those previously reported.¹¹²

***tert*-Butyl 2-oxo-2-phenylacetate (18)**¹¹³

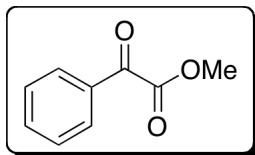


A solution of oxalyl chloride (2.0 mL, 24 mmol, 1 equiv.) in anhydrous THF (62 mL, 0.38 M) was cooled to 0 °C under inert atmosphere. *Tert*-butanol was added and the resulting reaction mixture was stirred for 1 h at 0 °C. Imidazole (4.82 g, 70.8 mmol, 3 equiv.) dissolved in THF (2.0 mL) was added via drop-funnel over 30 min, stirred for an additional 15 min at the 0 °C. The reaction was then warmed up to rt, then filtered. The resulting filtrate was concentrated to yield *tert*-butyl 2-(1*H*-imidazol-1-yl)-2-oxoacetate as a yellow oil (4.60 g, 99% yield). ¹H NMR (500 MHz, CDCl₃) δ 8.38 (s, 1H), 7.62 (t, *J* = 1.4 Hz, 1H), 7.15-7.14 (m, 1H), 1.64 (s, 9H).

2-(1*H*-imidazol-1-yl)-2-oxoacetyl chloride (1.65 g, 8.43 mmol, 1 equiv.) was dissolved in anhydrous THF (26 mL, 0.33 M) and cooled to -78 °C, under inert atmosphere. A solution of phenyl magnesium bromide (8.4 mL, 8.43 mmol, 1 equiv., 1.0 M in THF) was added and the reaction mixture was stirred for 1 h at -78 °C, then warmed up to rt over 2 h. The reaction was quenched with a saturated aqueous solution of NH₄Cl (10 mL). The organic extract was separated, and the resulting aqueous layer was extracted with diethyl ether (2 × 10 mL). The combine organic extracts was washed with brine (20 mL), dried over Na₂SO₄, then concentrated under reduced pressure. The crude product was purified by column chromatography (10% ethyl acetate in hexanes, *R_f* = 0.43) to yield the product as a yellow oil (425 mg, 24% yield). Spectral data matched those previously reported.¹¹³ ¹H NMR (500 MHz, CDCl₃) δ 7.98 (d, *J* = 7.6 Hz, 2H), 7.65 (t, *J* = 7.4, 7.4 Hz, 1H), 7.51 (t, *J* = 7.8, 7.8 Hz, 2H), 1.64 (s, 9H).

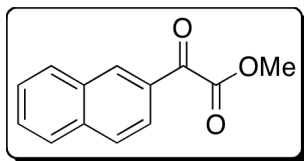
Representative procedure for the synthesis on α -ketoester acceptors for the Cross-Benzoin Reaction (68a-d)

Methyl 2-oxo-2phenylacetate (26a)



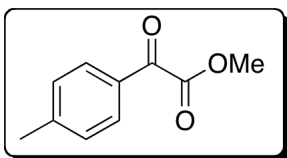
A solution of phenyl magnesium bromide in THF (30.5 mL, 30.5 mmol, 1.2 equiv.) was added to a solution of dimethyl oxalate (3.00 g, 25.4 mmol, 1 equiv.) in anhydrous diethyl ether (85 mL, 0.3 M) at -78 °C, under inert atmosphere. The reaction was warmed up to rt over 16 h, then quenched with a saturated aqueous solution of NH_4Cl (30 mL). The organic extract was separated, and the resulting aqueous layer was extracted with diethyl ether (2×30 mL). The combine organic extracts was washed with brine (100 mL), dried over Na_2SO_4 , then concentrated under reduced pressure. The crude product was purified by bulb-to-bulb distillation (130 °C at 2 Torr) to yield the product as a light yellow oil (2.36 g, 57% yield). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.02 (d, $J = 7.4$ Hz, 2H), 7.67 (t, $J = 7.2$ Hz, 1H), 7.52 (t, $J = 7.6$ Hz, 2H), 3.98 (s, 3H). Spectral data matched those previously reported.¹¹²

Methyl 2-(naphthalene-2-yl)-2-oxoacetate (26b)



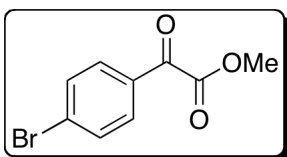
Yellow oil (331 mg, 36% yield). $R_f = 0.17$ (10% diethyl ether in hexanes). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.53 (s, 1H), 8.01 (d, $J = 8.6$ Hz, 1H), 8.95 (d, $J = 15.4$ Hz, 1H), 7.85 (dd, $J = 19.0, 8.5$ Hz, 2H), 7.61 (dd, $J = 7.0, 7.0$ Hz, 1H), 7.53 (dd, $J = 7.1, 7.1$ Hz, 1H), 4.01 (s, 3H). Spectra data matched those previously reported.¹¹¹

Methyl 2-oxo-2-*p*-tolylacetate (26c)



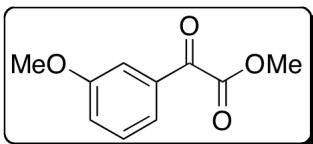
Crude product was purified by bulb-to-bulb distillation (105 °C at 2 Torr) to yield the product as a yellow oil (328 mg, 35% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.92 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 3.97 (s, 3H), 2.44 (s, 3H). Spectra data matched those previously reported.¹¹⁴

Methyl 2-(4-bromophenyl)-2-oxoacetate (26d)



White solid (345 mg, 37% yield). *R*_f = 0.14 (10% diethyl ether in hexanes). ¹H NMR (500 MHz, CDCl₃) δ 7.92 (d, *J* = 8.8 Hz, 2H), 7.67 (d, *J* = 9.0 Hz, 2H), 3.98 (s, 3H). Spectra data matched those previously reported.¹¹⁴

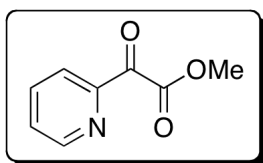
Synthesis of Methyl 2-(3-methoxyphenyl)-2-oxoacetate (26e)



3-Bromo anisole (500 μL, 3.95 mmol, 1 equiv.) was added dropwise to powder magnesium metal (99 mg, 4.07 mmol, 1.03 equiv.) in anhydrous THF (10 mL) at rt, under inert atmosphere. After stirring for 1 h, the Grignard reagent was added dropwise to a solution of dimethyl oxalate (700 mg, 5.93 mmol, 1.5 equiv.) in anhydrous THF (10 mL) at -78 °C. After stirring at -78 °C for 1 h, the reaction was warmed up to rt over 20 h. The reaction was quenched with a saturated aqueous solution of NH₄Cl (10 mL). The organic extract was separated, and the resulting aqueous layer was extracted with diethyl ether (2×10 mL). The combine organic extracts was washed with brine (20 mL), dried over Na₂SO₄, then concentrated under reduced pressure. The crude product was purified by

column chromatography (10% ethyl acetate in hexanes, R_f = 0.24) to yield the product as an orange oil (229 mg, 30% yield). **FTIR** (KBr film) ν_{\max} (cm^{-1}): 2957, 1741, 1688, 1598, 1583, 1487, 1466, 1454, 1432, 1318, 1291, 1254, 1198, 1169, 1157, 1046, 1020, 994, 759, 680; **^1H NMR** (500 MHz, CDCl_3) δ 7.52 (d, J = 7.8 Hz, 1H), 7.47 (s, 1H), 7.36 (t, J = 8.0 Hz, 1H), 7.15 (dd, J = 8.0, 2.1 Hz, 1H), 3.92 (s, 3H), 3.80 (s, 3H); **^{13}C NMR** (125 MHz, CDCl_3) – δ 186.0, 164.1, 160.0, 133.7, 130.0, 123.2, 121.9, 113.4, 55.5, 52.8; **HRMS** (EI^+) m/z calculated for $\text{C}_{10}\text{H}_{10}\text{O}_4$ $[\text{M}]^+$: 194.0579 found: 194.0578.

Synthesis of Methyl 2-oxo-2-(pyridin-2-yl)acetate (26f)

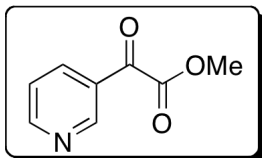


A solution of $n\text{BuLi}$ (2.5 mL, 5.34 mmol, 1.02 equiv., 2.12 M in hexanes) was added dropwise to a solution of 2-bromopyridine (500 μL , 5.24 mmol, 1 equiv.) in THF (17 mL) at $-78\text{ }^\circ\text{C}$, under inert atmosphere. After 30 min, the solution was transferred via cannula to a stirring solution of dimethyl oxalate (2.17 g, 18.3 mmol, 3.5 equiv.) at $0\text{ }^\circ\text{C}$. The reaction was allowed to stir at $0\text{ }^\circ\text{C}$ for 2 h, then quenched with a saturated aqueous solution of NH_4Cl (10 mL). The organic extract was separated, and the resulting aqueous layer was extracted with diethyl ether ($2 \times 10\text{ mL}$). The combine organic extracts was washed with brine (20 mL), dried over Na_2SO_4 , then concentrated under reduced pressure. The crude product was purified by column chromatography (20% ethyl acetate in hexanes, R_f = 0.15) to yield the product as a yellow oil (71 mg, 8% yield). **FTIR** (KBr film) ν_{\max} (cm^{-1}): 3058, 3011, 2957, 2849, 2362, 2337, 1747, 1712, 1585, 1434, 1325, 1288, 1212, 1091, 1009, 744, 695, 616; **^1H NMR** (500 MHz, CDCl_3) δ 8.74 (d, J = 4.7 Hz, 1H), 8.09 (d, J = 7.8 Hz, 1H), 7.90 (dddd, J = 9.2, 7.7, 7.7, 1.5 Hz, 1H), 7.56-7.53 (m, 1H), 4.00 (s, 3H);

^{13}C NMR (125 MHz, CDCl_3) – δ 187.7, 165.8, 150.4, 150.0, 137.4, 128.5, 123.6, 52.8;

HRMS (CI^+/NH_3) m/z calculated for $\text{C}_8\text{H}_7\text{N}_3$ $[\text{M}]^+$: 166.0504 found: 166.0501.

Synthesis of Methyl 2-oxo-2-(pyridin-3-yl)acetate (26g)



A solution of 3-bromopyridine (500 μL , 5.12 mmol, 1 equiv.) in THF (6.5 mL) was added dropwise to a solution of $n\text{BuLi}$ (2.5 mL, 5.27 mmol, 1.03 equiv., 2.12 M in hexanes) in THF (10 mL) at -78°C , under inert atmosphere. The reaction was stirred for 30 min at the same temperature. The lithiated pyridine was then transferred via cannula to a solution of dimethyl oxalate (2.30 g, 19.5 mmol, 3.8 equiv.) in THF (4.5 mL) at 0°C , the resulting reaction mixture was then allowed to warm up to rt over 20 h. The reaction was quenched with acetic acid (4 mL), then poured into distilled water (10 mL), the pH of the mixture was adjusted to 7 with saturated aqueous solution of NaHCO_3 . The organic extract was separated, the resulting aqueous layer was extracted with ethyl acetate ($\times 2$). The combined organic extract was washed with brine, dried over Na_2SO_4 then concentrated under reduced pressure. The crude product was purified by column chromatography (33% ethyl acetate in hexanes, $R_f = 0.15$) to yield the product as a light yellow oil (106 mg, 13% yield). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3086, 3062, 3029, 2955, 1748, 1730, 1497, 1454, 1435, 1422, 1360, 1255, 1215, 1139; **^1H NMR** (500 MHz, CDCl_3) δ 9.23 (d, $J = 1.7$ Hz, 1H), 8.83 (dd, $J = 4.8, 1.5$ Hz, 1H), 8.33 (dt, $J = 3.8, 1.9$ Hz, 1H), 7.44 (dd, $J = 7.9, 4.9$ Hz, 1H), 3.97 (s, 3H); **^{13}C NMR** (125 MHz, CDCl_3) – δ 184.4, 162.7, 155.0, 151.7, 137.4, 128.6, 123.9, 53.3; **HRMS** (EI^+) m/z calculated for $\text{C}_8\text{H}_7\text{NO}_3$ $[\text{M}]^+$: 165.0426, found: 165.0420.

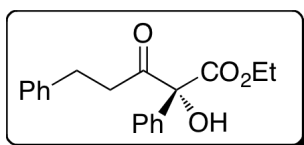
Et₃N (1.9 mL, 13.4 mmol) was added to CuI (128 mg, 0.670 mmol) in anhydrous THF (67 mL, 0.2 M) at rt, under inert atmosphere. The reaction was stirred at rt until a colourless clear solution is formed, the phenyl alkyne (740 μ L, 6.74 mmol), followed by ethyl oxalyl chloride (1.5 mL, 13.4 mmol) was added and the reaction was allowed to stir at rt for 2 h. The reaction was then quenched with sat. NaHCO₃ (aq), organic layer separated, and the resulting aqueous layer was extracted with Et₂O (3 \times 10 mL). The combined organic extract was dried over Na₂SO₄, then concentrated. The crude product was purified by column chromatography (10% ethyl acetate in hexanes, R_f = 0.23) to yield the product as an orange oil (66 mg, 4%, yield). ¹H NMR (500 MHz, CDCl₃) δ 7.70 (d, *J* = 7.3 Hz, 2H), 7.56-7.51 (m, 1H), 7.45 (t, *J* = 7.7, 7.7 Hz, 2H), 4.44 (q, *J* = 7.1, 7.1, 7.1 Hz, 2H), 1.45 (t, *J* = 7.1, 7.1 Hz, 3H). Spectral data matched those previously reported.¹¹⁵

General procedure for the NHC-catalyzed cross-benzoin reaction of aliphatic aldehydes and α -ketoesters

Aliphatic aldehyde (1.5 equiv.) was added to a suspension of the appropriate α -ketoester (1 equiv.), (*S*)-5-isopropyl-2-(perfluorophenyl)-6,8-dihydro-5*H*-[1,24]triazoleo[3,4-*c*]oxazin-2-ium tetrafluoroborate (**7ah**) (0.1 equiv.), and 4Å powered molecular sieves (1:1 w/w, α -ketoester/4Å MS) in anhydrous CH₂Cl₂ (0.2 M) at rt, under inert atmosphere. After stirring at rt for 10 min, *i*Pr₂NEt (1 equiv.) was added and the reaction was monitored by TLC. The reaction was quenched with AcOH (10 μ L), the reaction mixture was filtered through a short pipette column of silica (~1.5 inches), washed with EtOAc,

then concentrated under reduced pressure. The crude product was purified by column chromatography to yield the cross-benzoin product.

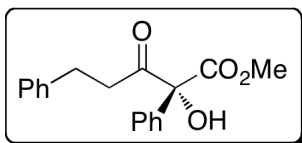
(+)-(R)-Ethyl 2-hydroxy-3-oxo-2,5-diphenylpentanoate (65a)



Light yellow oil (28 mg, 61% yield). $R_f = 0.27$ (20% hexanes in dichloromethane); 89% ee; $[\alpha]_D^{23} = +8.3$ (c 1.2, CHCl_3);

HPLC analysis – Chiralcel IA column, 5% isopropanol in hexanes, 1.0 mL/min. Major: 11.1 min, minor: 10.2 min. **^1H NMR** (500 MHz, CDCl_3) δ 7.52-7.50 (m, 2H), 7.38-7.35 (m, 3H), 7.25-7.22 (m, 2H), 7.18-7.15 (m, 1H), 7.08 (d, $J = 7.3$ Hz, 2H), 4.35-4.15 (m, 2H), 3.00-2.72 (m, 4H), 1.30 (t, $J = 7.1$, 7.1 Hz, 3H). Spectral data matched those previously reported.²⁴

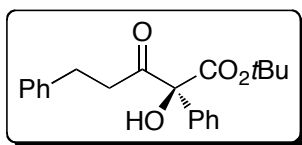
(+)-(R)-Methyl 2-hydroxy-3-oxo-2,4-diphenylbutanoate (66a)



Colourless oil (35 mg, 80% yield). $R_f = 0.14$ (20% hexanes in dichloromethane); 91% ee; $[\alpha]_D^{22} = +7.8$ (c 1.5, CHCl_3);

HPLC analysis – Chiralcel IA column, 5% isopropanol in hexanes, 1.0 mL/min. Major: 12.5 min, minor: 11.7 min. **FTIR** (KBr film) ν_{max} (cm^{-1}): 3473, 3062, 3028, 2954, 2927, 1727, 1496, 1451, 1436, 1404, 1361, 1263, 1192, 1125, 1071, 1030, 1003, 974, 752, 700; **^1H NMR** (500 MHz, CDCl_3) δ 7.60-7.40 (m, 2H), 7.42-7.35 (m, 3H), 7.26-7.16 (m, 3H), 7.08-7.07 (m, 2H), 4.71 (br s, 1H), 3.83 (s, 3H), 2.95-2.84 (m, 4H); **^{13}C NMR** (125 MHz, CDCl_3) – δ 205.1, 171.1, 140.6, 136.0, 129.0, 128.7, 128.5, 126.5, 126.3, 84.7, 53.8, 39.1, 30.1; **HRMS** (EI^+) m/z calculated for $\text{C}_{18}\text{H}_{18}\text{O}_4$ $[\text{M}]^+$: 298.1205 found: 298.1209.

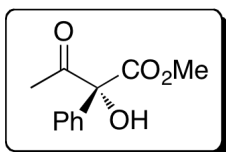
(+)-(R)-tert-Butyl 2-hydroxy-3-oxo-2,5-diphenylpentanoate (67)



Colourless oil (10 mg, 22% yield). $R_f = 0.24$ (20% hexanes in dichloromethane); 74% ee; $[\alpha]_D^{22} = +21$ (c 0.84, CHCl_3);

HPLC analysis – Chiralcel IC column, 5% isopropanol in hexanes, 1.0 mL/min. Major: 6.8 min, minor: 7.3 min. **FTIR** (KBr film) ν_{max} (cm^{-1}): 3466, 3062, 3028, 3003, 2979, 2932, 1722, 1496, 1450, 1395, 1370, 1283, 1155, 1124, 1070 1031, 840, 748, 699; **^1H NMR** (500 MHz, CDCl_3) δ 7.52 (d, $J = 6.4$ Hz, 2H), 7.30-7.36 (m, 3H), 7.24-7.19 (m, 2H), 7.17-7.15 (m, 1H), 7.09 (d, $J = 7.2$ Hz, 2H), 4.58 (s, 1H), 2.91-2.83 (m, 4H), 1.46 (s, 9H); **^{13}C NMR** (125 MHz, CDCl_3) – δ 205.1, 169.7, 140.9 136.4, 128.6, 128.5, 128.4, 128.1, 126.3, 84.8, 84.5, 39.3, 30.1, 28.0, 28.0; **HRMS** (EI^+) m/z calculated for $\text{C}_{21}\text{H}_{28}\text{NO}_4$ $[\text{M}]^+$: 358.2018 found: 358.2024.

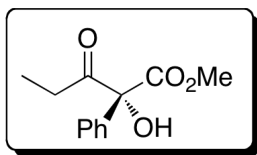
(-)-(R)-Methyl 2-hydroxy-3-oxo-2-phenylbutanoate (66b)



Colourless oil (28 mg, 88% yield). $R_f = 0.08$ (20% hexanes in dichloromethane); 30% ee; $[\alpha]_D^{22} = -11$ (c 1.4, CHCl_3); HPLC

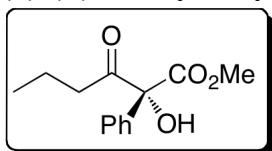
analysis – Chiralcel IC column, 2.5% isopropanol in hexanes, 1.0 mL/min. Major: 17.9 min, minor: 17.2 min. **FTIR** (KBr film) ν_{max} (cm^{-1}): 3472, 3063, 3031, 2956, 2850, 1718, 1601, 1494, 1450, 1436, 1355, 1258, 1169, 1107, 1073; **^1H NMR** (500 MHz, CDCl_3) δ 7.55-7.54 (m, 2H), 7.41-7.36 (m, 3H), 4.76 (s, 1H), 3.86 (s, 3H), 2.24 (s, 3H); **^{13}C NMR** (125 MHz, CDCl_3) – δ 203.8, 171.0, 136.2, 129.0, 128.8, 126.5, 84.9, 53.8, 25.3; **HRMS** (EI^+) m/z calculated for $\text{C}_{11}\text{H}_{12}\text{O}_4$ $[\text{M}]^+$: 208.0736 found: 208.0720.

(-)-(R)-Methyl 2-hydroxy-3-oxo-2-phenylpentanoate (66c)



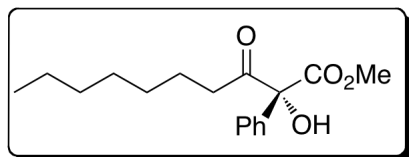
Colourless oil (28 mg, 82% yield). $R_f = 0.08$ (20% hexanes in dichloromethane); 91% ee; $[\alpha]_D^{21} = -14$ (c 1.0, CHCl_3); HPLC analysis – Chiralcel IC column, 5% isopropanol in hexanes, 1.0 mL/min. Major: 10.0 min, minor: 9.0 min. **FTIR** (KBr film) ν_{max} (cm^{-1}): 3474, 3062, 3030, 2980, 2955, 2942, 2882, 1727, 1494, 1450, 1437, 1379, 1346, 1262, 1191, 1128, 1075, 972, 753, 701; **^1H NMR** (500 MHz, CDCl_3) δ 7.53 (m, 2H), 7.40-7.34 (m, 3H), 2.70-2.64 (m, 1H), 2.57-2.41 (m, 1H), 1.01 (t, $J = 7.2$ Hz, 3H); **^{13}C NMR** (125 MHz, CDCl_3) – δ 207.0, 171.2, 136.4, 128.9, 128.7, 126.5, 84.7, 53.8, 30.9, 8.20; **HRMS** (EI^+) m/z calculated for $\text{C}_{12}\text{H}_{14}\text{O}_4$ $[\text{M}]^+$: 222.0892 found: 222.0888.

(-)-(R)-Methyl 2-hydroxy-3-oxo-2-phenylhexanoate (66d)



Colourless oil (34 mg, 92% yield). $R_f = 0.20$ (20% hexanes in dichloromethane); 91% ee; $[\alpha]_D^{21} = -11$ (c 1.1, CHCl_3); HPLC analysis – Chiralcel IA column, 5% isopropanol in hexanes, 1.0 mL/min. Major: 7.2 min, minor: 6.9 min. **FTIR** (KBr film) ν_{max} (cm^{-1}): 3475, 3062, 2963, 2935, 2876, 1727, 1494, 1450, 1437, 1404, 1361, 1262, 1191, 1134, 1033, 1009, 981, 746, 701; **^1H NMR** (500 MHz, CDCl_3) δ 7.53 (d, $J = 7.0$ Hz, 2H), 7.40-7.33 (m, 3H), 4.77 (s, 1H), 3.85 (s, 3H), 2.64-2.57 (m, 1H), 2.53-2.38 (m, 1H), 1.61-1.48 (m, 2H), 0.81 (t, $J = 7.4$, 7.4 Hz, 3H); **^{13}C NMR** (125 MHz, CDCl_3) – δ 206.1, 171.2, 136.3, 128.9, 128.7, 126.6, 84.7, 53.7, 39.3, 17.5, 13.6; **HRMS** (EI^+) m/z calculated for $\text{C}_{13}\text{H}_{16}\text{O}_4$ $[\text{M}]^+$: 236.1049 found: 236.1042.

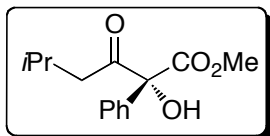
(-)-(R)-Methyl 2-hydroxy-3-oxo-2-phenyldecanoate (66e)



Colourless oil (44 mg, 98% yield). $R_f = 0.17$ (20% hexanes in dichloromethane); 93% ee; $[\alpha]_D^{21} = -11$ (c 1.1, CHCl_3); HPLC analysis – Chiralcel IC column,

5% isopropanol in hexanes, 1.0 mL/min. Major: 9.0 min, minor: 8.6 min. **FTIR** (KBr film) ν_{max} (cm^{-1}): 3479, 3030, 2955, 2928, 2857, 1728, 1494, 1450, 1437, 1404, 1365, 1262, 1192, 1129, 1070, 1034, 1011, 980, 746, 700; **^1H NMR** (500 MHz, CDCl_3) δ 7.56 (d, $J = 6.9$ Hz, 2H), 7.45-7.34 (m, 3H), 4.81 (s, 1H), 3.87 (s, 3H), 2.62-2.54 (m, 2H), 1.58-1.47 (m, 2H), 1.31-1.16 (m, 8H), 0.87 (t, $J = 6.9$, 6.9 Hz, 3H); **^{13}C NMR** (125 MHz, CDCl_3) – δ 206.3, 171.2, 128.9, 128.7, 126.6, 84.8, 53.7, 37.4, 31.8, 29.1, 29.0, 24.0, 22.7, 14.2; **HRMS** (EI^+) m/z calculated for $\text{C}_{17}\text{H}_{24}\text{O}_4$ $[\text{M}]^+$: 292.1675 found: 292.1675.

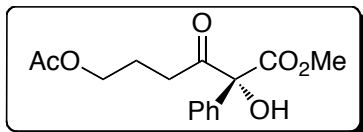
(-)-(R)-Methyl 2-hydroxy-5-methyl-3-oxo-2-phenylhexanoate (66g)



Colourless oil (18 mg, 43% yield). $R_f = 0.28$ (20% hexanes in dichloromethane); 97% ee; $[\alpha]_D^{21} = -9.9$ (c 0.96, CHCl_3);

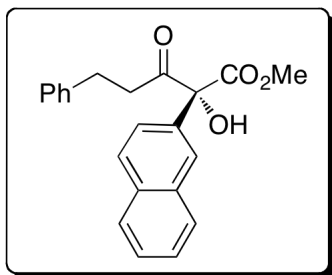
HPLC analysis – Chiralcel IC column, 5% isopropanol in hexanes, 1.0 mL/min. Major: 9.6 min, minor: 9.2 min. **FTIR** (KBr film) ν_{max} (cm^{-1}): 3475, 3062, 2958, 2934, 2873, 1726, 1494, 1467, 1450, 1436, 1402, 1386, 1368, 1260; **^1H NMR** (500 MHz, CDCl_3) δ 7.754-7.53 (m, 2H), 7.40-7.34 (m, 3H), 4.77 (s, 1H), 3.85 (s, 3H), 2.47 (dddd, $J = 17.6$, 17.6, 17.6, 7.0 Hz, 2H), 2.11-2.06 (m, 1H), 0.83 (d, $J = 6.7$ Hz, 3H), 0.76 (d, $J = 6.7$ Hz, 3H); **^{13}C NMR** (125 MHz, CDCl_3) – δ 205.5, 171.2, 136.1, 128.9, 128.6, 126.6, 84.8, 53.7, 46.0, 24.4, 22.5, 22.4; **HRMS** (EI^+) m/z calculated for $\text{C}_{14}\text{H}_{18}\text{O}_4$ $[\text{M}]^+$: 250.1205, found: 250.1206.

(+)-(R)-Methyl 6 acetoxy-2-hydroxy-3-oxo-2-phenylhexanoate (66i)



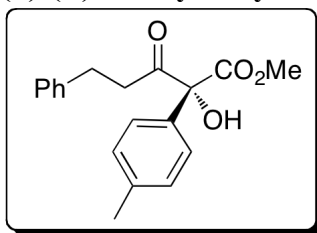
Yellow oil (27 mg, 56% yield). $R_f = 0.16$ (100% dichloromethane); 94% ee; $[\alpha]_D^{21} = +10$ (c 0.98, CHCl_3); HPLC analysis – Chiralcel IC column, 5% isopropanol in hexanes, 1.0 mL/min. Major: 39.2 min, minor: 41.4 min. **FTIR** (KBr film) ν_{max} (cm^{-1}): 3457, 3030, 1733, 1388, 1365, 1108; **^1H NMR** (500 MHz, CDCl_3) δ 7.54-7.52 (m, 2H), 7.41-7.36 (m, 3H), 4.72 (s, 1H), 3.96 (t, $J = 6.4$, 6.4 Hz, 2H), 3.85 (s, 3H), 2.72-2.61 (m, 2H), 1.96 (s, 3H), 1.86 (dddd, $J = 13.5$, 6.9, 6.9, 6.9 Hz, 2H); **^{13}C NMR** (125 MHz, CDCl_3) – δ 205.3, 171.1, 171.1, 136.0, 129.0, 128.7, 126.4, 84.7, 63.4, 53.9, 33.8, 23.1 21.0; **HRMS** (Cl^+/NH_3) m/z calculated for $\text{C}_{15}\text{H}_{22}\text{NO}_6$ $[\text{M}+\text{NH}_4]^+$: 312.1447, found: 312.1456.

(+)-(R)-Methyl 2-hydroxy-2-(naphthalen-2-yl)-3-oxo-5-phenylpentanoate (66m)



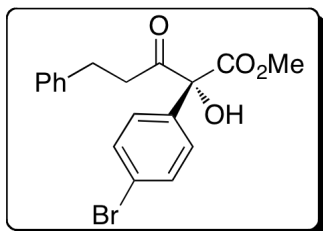
Colourless oil (20 mg, 46% yield). $R_f = 0.24$ (20% hexanes in dichloromethane); 85% ee; $[\alpha]_D^{22} = +20$ (c 1.3, CHCl_3); HPLC analysis – Chiralcel IB column, 5% isopropanol in hexanes, 1.0 mL/min. Major: 9.2 min, minor: 8.7 min.; **FTIR** (KBr film) ν_{max} (cm^{-1}): 3472, 3060, 3027, 2953, 2927, 1726, 1602, 14997, 1454, 1436, 1360, 1267, 1246, 1207, 1162, 1117, 819, 749, 699; **^1H NMR** (500 MHz, CDCl_3) δ 8.00 (s, 1H), 7.84-7.81 (m, 3H), 7.55-7.49 (m, 3H), 7.20-7.04 (m, 3H), 7.05 (d, $J = 7.0$ Hz, 2H), 4.81 (s, 1H), 3.85 (s, 3H), 3.06-2.76 (m, 4H); **^{13}C NMR** (125 MHz, CDCl_3) – δ 205.2, 171.2, 140.6, 133.4, 133.4, 133.1, 128.7, 128.6, 128.5, 127.8, 127.0, 126.7, 126.3, 126.0, 124.0, 84.9, 53.9, 39.2, 30.0; **HRMS** (EI^+) m/z calculated for $\text{C}_{22}\text{H}_{20}\text{O}_4$ $[\text{M}]^+$: 348.1362 found: 348.1364.

(+)-(R)-Methyl 2-hydroxy-3-oxo-5-phenyl-2 *p*-tolylpentanoate (66n)



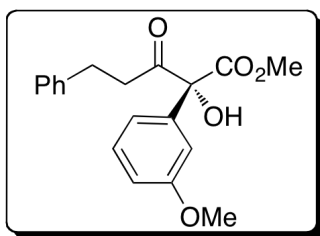
Colourless oil (20 mg, 47% yield). $R_f = 0.13$ (20% hexanes in dichloromethane); 95% ee; $[\alpha]_D^{21} = +2.4$ (c 0.85, CHCl_3); HPLC analysis – Chiralcel IB column, 5% isopropanol in hexanes, 1.0 mL/min. Major: 8.7 min, minor: 8.4 min. **FTIR** (KBr film) ν_{max} (cm^{-1}): 3474, 3028, 2954, 2924, 1727, 1512, 1497, 1454, 1437, 1407, 1361, 1263, 1195, 1180, 1131, 1101, 1030, 819, 747, 699; **^1H NMR** (500 MHz, CDCl_3) δ 7.35 (d, $J = 8.2$ Hz, 2H), 7.24-7.21 (m, 2H), 7.18-7.15 (m, 3H), 7.08 (d, $J = 7.2$ Hz, 2H), 4.68 (s, 1H), 3.82 (s, 3H), 3.02-2.91 (m, 1H), 2.89-2.81 (m, 3H), 2.35 (s, 3H); **^{13}C NMR** (125 MHz, CDCl_3) – δ 205.4, 171.2, 140.7, 138.9, 133.1, 129.4, 128.6, 128.5, 126.4, 126.3, 84.7, 53.8, 39.1, 30.1, 21.3; **HRMS** (EI^+) m/z calculated for $\text{C}_{19}\text{H}_{20}\text{O}_4$ $[\text{M}]^+$: 312.1362 found: 312.1366.

(+)-(R)-Methyl 2-(4-bromophenyl)-2-hydroxy-3-oxo-5-phenylpentanoate (66o)



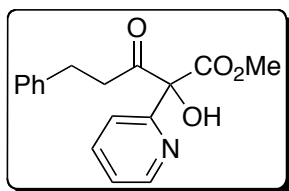
White solid (42 mg, 92% yield). $R_f = 0.13$ (20% hexanes in dichloromethane); 91% ee; $[\alpha]_D^{21} = +17$ (c 1.1, CHCl_3); HPLC analysis – Chiralcel IB column, 5% isopropanol in hexanes, 1.0 mL/min. Major: 9.7 min, minor: 9.3 min. **m.p.**: 63-64 °C; **FTIR** (KBr film) ν_{max} (cm^{-1}): 3472, 3028, 2954, 1728, 1487, 1454, 1437, 1399, 1360, 1262, 1190, 1129, 1094, 1075, 1029, 1011, 824, 789, 699; **^1H NMR** (500 MHz, CDCl_3) δ 7.51 (d, $J = 8.2$ Hz, 2H), 7.36 (d, $J = 8.6$ Hz, 2H), 7.27-7.16 (m, 3H), 7.06 (d, $J = 7.1$ Hz, 2H), 4.65 (s, 1H), 3.81 (s, 3H), 2.99-2.76 (m, 4H); **^{13}C NMR** (125 MHz, CDCl_3) – δ 204.4, 170.7, 140.5, 134.8, 131.8, 128.6, 128.5, 128.3, 126.4, 123.3, 84.3, 54.0, 39.0, 30.0; **HRMS** (EI^+) m/z calculated for $\text{C}_{18}\text{H}_{17}\text{BrO}_4$ $[\text{M}]^+$: 376.031 found: 376.0297.

(+)-(R)-Methyl 2-hydroxy-2-(3-methoxyphenyl)-3-oxo-5-phenylpentanoate (66p)



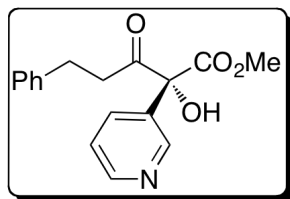
Colourless oil (26 mg, 74% yield). $R_f = 0.60$ (20% diethyl ether in dichloromethane); 91% ee; $[\alpha]_D^{22} = +10$ (c 1.3, CHCl_3); HPLC analysis – Chiralcel IB column, 10% isopropanol in hexanes, 1.0 mL/min. Major: 12.0 min, minor: 10.6 min. ; **FTIR** (KBr film) ν_{max} (cm^{-1}): 3467, 3028, 2954, 1728, 1601, 1585, 1491, 1454, 1435, 1319, 1291, 1255, 1190, 1155, 1122, 1082, 1048, 778, 699; **^1H NMR** (500 MHz, CDCl_3) δ 7.31-7.24 (m, 3H), 7.20-7.17 (m, 1H), 7.11-7.06 (m, 4H), 6.92-6.90 (m, 1H), 4.75 (s, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 2.99-2.84 (m, 4H); **^{13}C NMR** (125 MHz, CDCl_3) – δ 205.0, 180.0, 160.0, 140.7, 137.5, 129.7, 128.6, 128.5, 126.3, 118.9, 114.6, 112.1, 84.6, 55.5, 53.8, 39.0, 30.1; **HRMS** (EI^+) m/z calculated for $\text{C}_{19}\text{H}_{20}\text{O}_5$ $[\text{M}]^+$: 328.1311 found: 328.1316.

Methyl 2-hydroxy-3-oxo-5-phenyl-2-(pyridin-2-yl)pentanoate (66q)



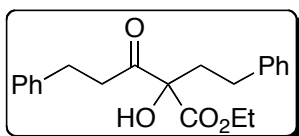
Yellow oil (14 mg, 28% yield). $R_f = 0.18$ (40% ethyl acetate in hexanes); 0% ee; HPLC analysis – Chiralcel IA column, 5% isopropanol in hexanes, 1.0 mL/min. 14.1 min and 16.2 min. **FTIR** (KBr film) ν_{max} (cm^{-1}): 3028, 2954, 2927, 1744, 1718, 1700, 1591, 1575, 1497, 1575, 1497, 1472, 1455, 1437, 1419; **^1H NMR** (500 MHz, CDCl_3) δ 8.63 (d, $J = 5.3$ Hz, 1H), 7.73 (dddd, $J = 9.5, 7.9, 7.9, 1.8$ Hz, 1H), 7.42 (d, $J = 8.1$ Hz, 1H), 7.32-7.27 (m, 3H), 7.22-7.18 (m, 3H), 6.13 (s, 1H), 3.77 (s, 3H), 3.04-2.96 (m, 2H), 2.89-2.75 (m, 2H); **^{13}C NMR** (125 MHz, CDCl_3) – δ 172.2, 168.6, 153.7, 150.0, 140.4, 137.4, 128.7, 128.7, 128.5, 128.5, 126.5, 124.2, 122.9, 75.6, 53.0, 35.6, 30.9; **HRMS** (EI^+) m/z calculated for $\text{C}_{17}\text{H}_{17}\text{NO}_4$ $[\text{M}]^+$: 299.1158 found: 299.1166.

(+)-(R)-Methyl 2-hydroxy-3-oxo-5-phenyl-2-(pyridin-2-yl)pentanoate (66r)



Reaction time = 1.5 h. Colourless oil (40 mg, 86% yield). $R_f = 0.15$ (20% diethyl ether in dichloromethane); 78% ee; $[\alpha]_D^{23} = +11$ (c 1.0, CHCl_3); HPLC analysis – Chiralcel IB column, 5% isopropanol in hexanes, 1.0 mL/min. Major: 32.8 min, minor: 29.5 min. **FTIR** (KBr film) ν_{max} (cm^{-1}): 3086, 3062, 3029, 2954, 1747, 1730, 1497, 1454, 1435, 1422, 1360, 1255, 1215, 1139, 1117, 1096, 1078, 1050, 1029; **^1H NMR** (500 MHz, CDCl_3) δ 8.83 (d, $J = 2.1$ Hz, 1H), 8.58 (dd, $J = 4.8, 1.5$ Hz, 1H), 7.87 (dddd, $J = 8.4, 3.8, 1.9, 1.9$ Hz, 1H), 7.30-7.23 (m, 3H), 7.20-7.17 (m, 1H), 7.10 (d, $J = 7.8$ Hz, 2H), 3.82 (s, 3H), 3.03-2.92 (m, 2H), 2.91-2.87 (m, 2H); **^{13}C NMR** (125 MHz, CDCl_3) – δ 204.1, 170.3, 149.7, 148.0, 140.4, 134.7, 131.8, 128.6, 128.5, 126.4, 123.3, 83.5, 54.1, 39.1, 29.8; **HRMS** (EI^+) m/z calculated for $\text{C}_{17}\text{H}_{17}\text{NO}_4$ $[\text{M}]^+$: 299.1158 found: 299.1164.

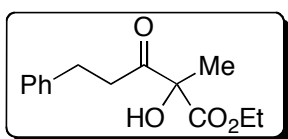
Ethyl 2-hydroxy-3-oxo-5-phenyl-2-(3-phenylpropanoyl)pentanoate (65b)



Cross-benzoin product **65d** was synthesized following the general procedure for the NHC-catalyzed cross benzoin reaction with triazolium salt **7k** (30 mol %) and $i\text{Pr}_2\text{NEt}$ (30 mol %). Light yellow oil (42 mg, 82% yield). $R_f = 0.35$ (20% hexanes in dichloromethane). 0% ee; HPLC analysis – Chiralcel IC column, 5% isopropanol in hexanes, 1.0 mL/min. $R_T = 11.0$ and 11.9 min. **FTIR** (KBr film) ν_{max} (cm^{-1}): 3484, 3063, 3028, 2980, 2932, 1719, 1604, 1497, 1454, 1397, 1367, 1250, 1193, 1157, 1104, 1074, 1057, 1030, 1017; **^1H NMR** (500 MHz, CDCl_3) δ 7.31-7.7.28 (m, 4H), 7.22-7.16 (m, 6H), 4.26 (s, 1H), 4.13 (dddd, $J = 7.1, 7.1, 7.1, 2.3$ Hz, 2H), 3.11-3.04 (m, 1H), 2.91 (dd, $J = 8.2, 8.2$ Hz, 2H), 2.87-2.81 (m, 1H),

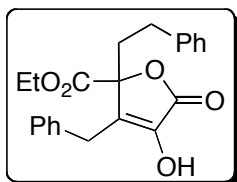
2.60 (dddd, $J = 10.3, 10.3, 5.4, 5.4$ Hz, 2H), 2.40 (dddd, $J = 13.9, 13.9, 9.9, 6.9$ Hz, 1H), 2.20 (dddd, $J = 16.2, 13.7, 10.9, 6.3$ Hz, 1H), 1.23 (t, $J = 7.4, 7.4$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) – δ 206.1, 171.0, 141.1, 140.7, 128.7, 128.7, 128.6, 128.6, 126.5, 126.3, 84.0, 62.9, 38.9, 37.1, 29.7, 29.6, 14.2; HRMS (EI^+) m/z calculated for $\text{C}_{21}\text{H}_{24}\text{O}_4$ $[\text{M}]^+$: 340.1675, found: 340.1680.

Ethyl 2-hydroxy-2-methyl-3-oxo-5-phenylpentanoate (65c)



Reaction was performed with 10 mol % of $i\text{Pr}_2\text{NEt}$. Reaction time = 16 h. Colourless oil (37 mg, 82% yield). $R_f = 0.15$ (100% dichloromethane); 0% ee; HPLC analysis – Chiralcel IC column, 2.5% isopropanol in hexanes, 1.0 mL/min. Retention times = 10.2 and 10.6 min. ^1H NMR (500 MHz, CDCl_3) δ 7.29-7.26 (m, 1H), 7.21-7.14 (m, 4H), 4.15 (dddd, $J = 7.2, 7.2, 7.2, 3.5$ Hz, 2H), 4.12 (s, 1H), 3.01 (m, 1H), 2.94-2.91 (m, 2H), 2.89-2.81 (m, 1H), 1.54 (s, 3H), 1.22 (t, $J = 6.6, 6.6$ Hz, 3H). Spectral data matched those previously reported.²⁴

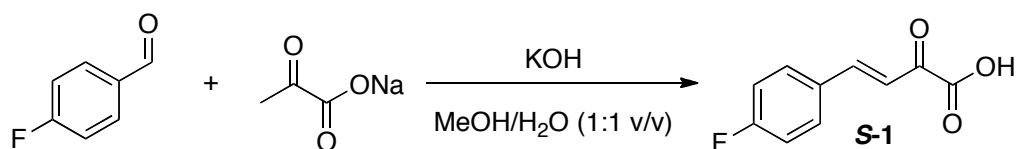
Ethyl 3-benzyl-4-hydroxy-5-oxo-2-phenethyl-2,5-dihydrofuran-2-carboxylate (68)



68 was synthesized using the general procedure for the NHC-catalyzed cross-benzoin reaction with triazolium catalyst **7k** (30 mol %) and $i\text{Pr}_2\text{NEt}$ (100 mol %). Colourless oil (17 mg, 35% yield). $R_f = 0.13$ (25% ethyl acetate in hexanes). FTIR (KBr film) ν_{max} (cm^{-1}): 3333, 3063, 3029, 2982, 2935, 1777, 1755, 1737, 1603, 1497, 1390, 1220, 1176, 1103, 1062, 1031, 968, 754, 702; ^1H NMR (500 MHz, CDCl_3) δ 7.34-7.25 (m, 7H), 7.21-7.18 (m, 1H), 7.00 (d, $J = 7.1$ Hz, 2H), 6.33 (br s, 1H), 3.96 (q, $J = 7.1, 7.1$ Hz, 2H), 3.70 (d, $J = 2.4$ Hz, 2H),

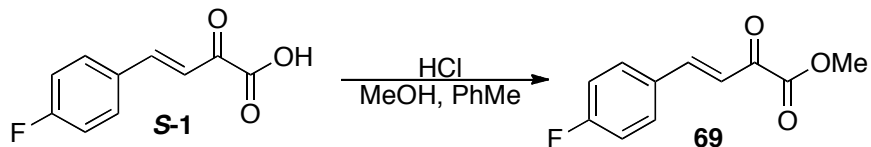
2.54-2.47 (m, 2H), 2.42-2.39 (m, 1H), 2.13 (dddd, $J = 15.8, 15.8, 13.8, 6.5$, 1H), 1.17 (t, $J = 7.1, 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) – δ 169.6, 168.1, 140.4, 139.5, 136.4, 131.4, 129.2, 128.9, 128.6, 128.6, 127.2, 126.4, 87.4, 62.7, 36.1, 30.2, 29.3, 14.0; HRMS (EI^+) m/z calculated for $\text{C}_{22}\text{H}_{22}\text{O}_5$ $[\text{M}]^+$: 366.1467 found: 366.1461.

(*E*)-4-(4-Fluorophenyl)-2-oxobut-3-enoic acid (*S*-1)



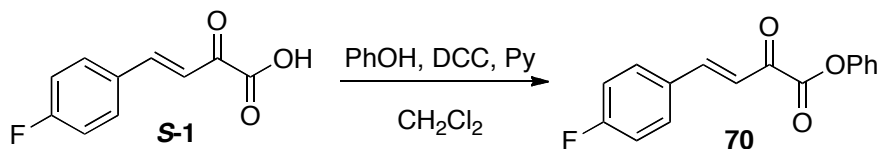
p-Fluorobenzaldehyde (1.0 mL, 9.32 mmol) was added to sodium pyruvate (1.03 g, 9.32 mmol) dissolved in MeOH/H₂O (2 mL, 1:1 v/v). The reaction was cooled to 0 °C for 5 min, then KOH (784 mg, 14.0 mmol) dissolved in MeOH/H₂O (7.3 mL, 1:1 v/v) was added dropwise. The reaction was kept at the same temperature for 4 h, quenched with HCl (1 M) until the reaction mixture reaches pH 2. The resulting aqueous solution was extracted with EtOAc (3 × 10 mL), the combined organic extracts was dried over Na₂SO₄, then concentrated under reduced pressure. The resulting crude product was triturated with hexanes to yield the pure product as a yellow solid (1.70 g, 94% yield). ^1H NMR (500 MHz, CDCl_3) δ 9.51 (br s, 1H), 8.12 (d, $J = 16.2$ Hz, 1H), 7.71 (dd, $J = 8.6, 5.3$ Hz, 2H), 7.54 (d, $J = 16.6$ Hz, 1H), 7.16 (dd, $J = 9.0, 9.0$ Hz, 2H). Spectral data matched those previously reported.¹¹⁶

(E)-Methyl 4-(4-fluorophenyl)-2-oxobut-3-enoate (69)



HCl (80 μ L, 0.976 mmol, 12.1 M) was added to α -ketoacid **S-1** in MeOH (4.3 mL, 105 mmol) and toluene (2.0 mL, 0.6 M) at rt. The reaction was refluxed at 110 $^{\circ}$ C for 3 h, then cooled to rt. The solvent was removed in vacuo to yield the pure product as a yellow solid (247 mg, 97% yield). **m.p.**: 88-90 $^{\circ}$ C; **FTIR** (KBr film) ν_{max} (cm^{-1}): 3073, 1727, 1688, 1610, 1599, 1587, 1510, 1435, 1417, 1321, 1301, 1290, 1264, 1226, 1199, 1186, 1157, 1091, 997; **^1H NMR** (500 MHz, CDCl_3) δ 7.85 (d, J = 15.8 Hz, 1H), 7.65 (dd, J = 8.6, 5.3 Hz, 2H), 7.32 (d, J = 16.1 Hz, 1H), 7.13 (dd, J = 8.4, 8.4 Hz, 2H), 3.94 (s, 3H); **^{13}C NMR** (125 MHz, CDCl_3) – δ 182.3, 165.0 (d, J = 255.3 Hz), 162.6, 147.4, 131.4 (d, J = 11.5 Hz), 130.5 (d, J = 3.4 Hz), 120.3 (d, J = 1.9 Hz), 116.5 (d, J = 22.1 Hz), 53.2; **HRMS** (EI^+) m/z calculated for $\text{C}_{11}\text{H}_9\text{O}_3\text{F}$ [M] $^+$: 208.0536, found: 208.0542.

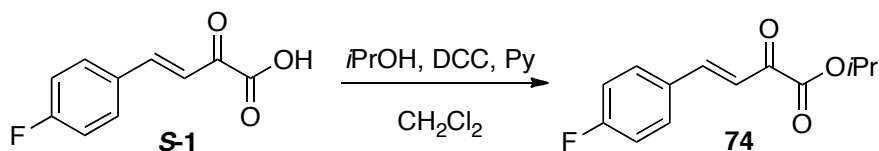
(E)-Phenyl 4-(4-fluorophenyl)-2-oxobut-3-enoate (70)



To a 3-neck flask equipped with a dropfunnel was added α -ketoacid **S-1** (284 mg, 1.46 mmol) and phenol (138 mg, 1.46 mmol). Anhydrous CH_2Cl_2 (4 mL), followed by pyridine (120 μ L, 1.46 mmol) was added, under inert atmosphere. The resulting solution was cooled to 0 $^{\circ}$ C for 5 min. DCC (331 mg, 1.61 mmol) dissolved in anhydrous CH_2Cl_2 (2 mL) was added drop-wise via the dropfunnel. The reaction mixture was stirred over

20 h, the white precipitated formed was filtered off, washed with CH₂Cl₂ (10 mL), the combined filtrate was collected and concentrated under reduced pressure. The crude product was purified by column chromatography (20% ethyl acetate in hexanes, *R_f* = 0.24) to yield the product as a yellow solid (247 mg, 63% yield). **m.p.**: 113-115 °C; **FTIR** (KBr film) ν_{max} (cm⁻¹): 1743, 1686, 1608, 1597, 1591, 1586, 1509, 1489, 1418, 1245, 1230, 1186, 1159, 1098; **¹H NMR** (500 MHz, CDCl₃) δ 7.94 (d, *J* = 16.1 Hz, 1H), 7.67 (dd, *J* = 9.0, 5.1 Hz, 2H), 7.45 (dd, *J* = 8.1, 8.1 Hz, 2H), 7.40 (d, *J* = 16.0 Hz, 1H), 7.31 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.14 (dd, *J* = 8.6, 8.6 Hz, 2H); **¹³C NMR** (125 MHz, CDCl₃) – δ 181.8, 165.1 (d, *J* = 253.8 Hz), 160.6, 150.5, 147.9, 131.5 (d, *J* = 9.1 Hz), 130.5 (d, *J* = 2.4 Hz), 129.9, 126.8, 121.4, 120.3 (d, *J* = 2.4 Hz), 116.7 (d, *J* = 22.1 Hz); **HRMS** (EI⁺) *m/z* calculated for C₁₆H₁₁O₃F [M]⁺: 270.0692, found: 270.0694.

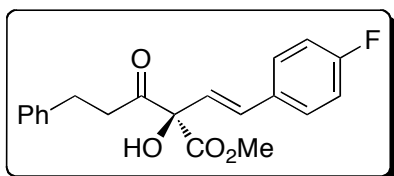
(*E*)-Isopropyl 4-(4-fluorophenyl)-2-oxobut-3-enoate (74)



α -Ketoester **74** was synthesized using the same procedure for the synthesis of **70**. Yellow oil (152 mg, 78% yield). *R_f* = 0.13 (10% ethyl acetate in hexanes). **FTIR** (KBr film) ν_{max} (cm⁻¹): 3076, 2985, 2938, 1724, 1695, 1666, 1598, 1508, 1467, 1456, 1417, 1388, 1376, 1360, 1314, 1290, 1232, 1157, 1072, 985; **¹H NMR** (500 MHz, CDCl₃) δ 7.81 (d, *J* = 16.1 Hz, 1H), 7.63 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.28 (d, *J* = 16.0 Hz, 1H), 7.12 (dd, *J* = 8.4, 8.4 Hz, 2H), 5.26-5.18 (m, 1H), 1.40 (d, *J* = 6.2 Hz, 6H); **¹³C NMR** (125 MHz, CDCl₃) – δ 183.2, 164.8 (d, *J* = 252.2 Hz), 162.0, 146.9, 131.2 (d, *J* = 8.8 Hz),

130.6 (d, $J = 3.8$ Hz), 120.6, 116.5 (d, $J = 22.0$ Hz) 70.9, 21.8; **HRMS** (EI^+) m/z calculated for $\text{C}_{13}\text{H}_{13}\text{O}_3\text{F}$ $[\text{M}]^+$: 236.0849, found: 236.0853.

(+)-(E)-Methyl 2-(4-fluorostyryl)-2-hydroxy-3-oxo-5-phenylpentanoate (72)

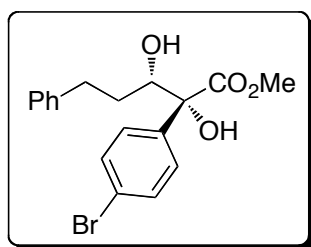


Anhydrous CH_2Cl_2 (550 μL , 0.2 M) was added to a dry mixture of acceptor **69** (23 mg, 0.110 mmol), triazolium salt **7ah** (9.3 mg, 0.0220 mmol), and 4Å powered molecular sieves (24 mg), under inert atmosphere. Hydrocinnamaldehyde (22 μL , 0.165 mmol) was added, the resulting suspension was stirred at rt for 10 min prior to the addition of Et_3N (11 μL , 0.110 mmol). The reaction was stirred at rt for 6 h, then quenched with AcOH (10 μL), filtered through a small pad of silica, washed with EtOAc (6 mL), then concentrated. The crude product was purified by column chromatography (20% hexanes in dichloromethane, $R_f = 0.14$) to yield the pure product as a yellow oil (17 mg, 45% yield). 67% ee; $[\alpha]_{\text{D}}^{23} = +16$ (c 1.5, CHCl_3); HPLC analysis – Chiralcel IA column, 5% isopropanol in hexanes, 1.0 mL/min. Major: 18.8 min, minor: 17.1 min. **FTIR** (KBr film) ν_{max} (cm^{-1}): 3472, 3064, 3029, 2955, 2925, 2854, 1725, 1726, 1603, 1510, 1498, 1454, 1437, 1414, 1360, 1277, 1229, 1204, 1159, 1094; **^1H NMR** (500 MHz, CDCl_3) δ 7.36-7.33 (m, 2H), 7.25-7.23 (m, 3H), 7.18-7.14 (m, 4H), 6.84 (d, $J = 16.0$ Hz, 1H), 6.49 (d, $J = 15.6$ Hz, 1H), 4.43 (s, 1H), 3.76 (s, 3H), 3.14-3.07 (m, 1H), 3.01-2.95 (m, 1H), 2.92 (ddd, $J = 7.8, 7.8, 7.8$ Hz, 2H); **^{13}C NMR** (125 MHz, CDCl_3) – δ 204.2, 170.5, 140.5, 132.1, 131.2, 128.8, 128.7, 128.6, 126.5, 123.6, 115.9, 115.7, 84.3, 53.9, 39.1, 29.9; **HRMS** (EI^+) m/z calculated for $\text{C}_{20}\text{H}_{19}\text{O}_4\text{F}$ $[\text{M}]^+$: 342.1267, found: 342.1262.

General procedure for the Reduction of Cross-Benzoin Product **66**

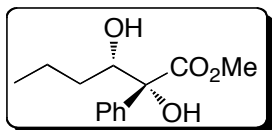
A solution of ZnCl₂ (1 equiv., 1.0 M in Et₂O) was added to solid NaBH₄ (1 equiv.) in dry THF at 0 °C, under inert atmosphere. Cross-benzoin product **66**, dissolved in dry THF (total concentration of 0.20 M with respect to **66**) was added and stirred at 0 °C until complete consumption of **66** was observed by TLC. The reaction was quenched by the slow addition of distilled water (~2 mL), the resulting aqueous solution was extracted with Et₂O (3×). The combined organic extracts were dried over Na₂SO₄, then concentrated under reduced pressure. The crude product was purified by flash column chromatography (25% ethyl acetate in hexanes).

(+)-(2*R*,3*S*)-Methyl 2-(4-bromophenyl)-2,3-dihydroxy-5-phenylpentanoate (*syn*-**78a**)



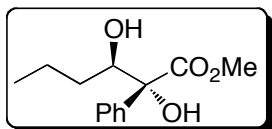
White solid (29 mg, 69% yield, >20:1 dr, *syn/anti*). $R_f = 0.10$ (25% ethyl acetate in hexanes); $[\alpha]_D^{21} = +7.1$ (c 1.1, CHCl₃). **m.p.**: 61-63 °C; **FTIR** (KBr film) ν_{\max} (cm⁻¹): 3489, 3062, 3026, 2955, 2859, 1732, 1487, 1454, 1437, 1397, 1304, 1261, 1178, 1132, 1098, 1075; **¹H NMR** (500 MHz, CDCl₃) δ 7.44 (d, $J = 8.6$ Hz, 2H), 7.39 (d, $J = 8.6$ Hz, 2H), 7.26-7.23 (m, 2H), 7.21-7.16 (m, 1H), 7.07 (d, $J = 7.2$ Hz, 2H), 4.26 (d, $J = 9.9$ Hz, 1H), 4.02 (s, 1H), 3.82 (s, 3H), 2.85-2.80 (m, 1H), 2.60-2.54 (1H), 2.13 (br s, 1H), 1.68-1.62 (m, 1H), 1.47-1.42 (m, 1H); **¹³C NMR** (125 MHz, CDCl₃) – δ 174.7, 141.6, 137.4, 131.8, 131.7, 128.7, 128.6, 127.6, 126.1, 122.5, 81.6, 54.0, 32.0; **HRMS** (CI⁺/NH₃) m/z calculated for C₁₈H₁₉BrO₄ [M+NH₄]⁺: 396.0810, found: 396.0807.

(+)-(2*R*,3*S*)-Methyl 2,3-dihydroxy-2-phenylhexanoate (*syn*-78b)



White solid (21 mg, 75% yield, 14:1 dr, *syn/anti*). R_f = 0.21 (25% ethyl acetate in hexanes); $[\alpha]_D^{21} = +14$ (c 1.0, CHCl_3). **m.p.**: 120-122 °C; **FTIR** (KBr film) ν_{max} (cm^{-1}): 3499, 2958, 2870, 1723, 1448, 1436, 1244, 1183, 1183, 1135, 1100, 1072; **^1H NMR** (500 MHz, CDCl_3) δ 7.61 (d, J = 7.4 Hz, 2H), 7.38-7.36 (m, 2H), 7.31-7.29 (m, 1H), 4.36-4.32 (m, 1H), 3.97 (s, 1H), 3.83 (s, 3H), 2.06 (d, J = 8.3 Hz, 1H), 1.51-1.50 (m, 1H), 1.33-1.25 (m, 2H), 1.09-1.07 (m, 1H), 0.81 (t, J = 7.3, 7.3 Hz, 3H); **^{13}C NMR** (125 MHz, CDCl_3) – δ 175.3, 138.6, 128.6, 128.2, 125.8, 81.9, 76.0, 53.8, 32.5, 19.2, 14.0; **HRMS** (TOF⁺) m/z calculated for $\text{C}_{13}\text{H}_{18}\text{O}_4$ $[\text{M}+\text{Na}]^+$: 261.1097, found: 261.1100.

(+)-(2*R*,3*R*)-Methyl 2,3-dihydroxy-2-phenylhexanoate (*anti*-78b)



NaBH_4 (4.8 mg, 0.13 mmol) was added to cross-benzoin product **66d** (30 mg, 0.13 mmol) in MeOH (640 μL , 0.20 M) at 0 °C, under inert atmosphere. The reaction was stirred until complete consumption of the starting material was observed by TLC (~1 h). The reaction was quenched with HCl (~1 mL, 1 M). The resulting aqueous solution was extracted with EtOAc (3 \times 5 mL). The combined organic extracts were dried over Na_2SO_4 , then concentrated under reduced pressure. The crude product was purified by column chromatography (25% ethyl acetate in hexanes, 1:1 dr, 22 mg, combined yield of 73%). *Syn*-**78b**: R_f = 0.21; *Anti*-**78b**: R_f = 0.18; 86% ee; HPLC analysis – Chiralcel ASH column, 4% isopropanol in hexanes, 1.0 mL/min. Major: 24.5 min, minor: 16.8 min.: $[\alpha]_D^{21} = +29$ (c 0.54, CH_2Cl_2). **m.p.**: 75-77 °C; **^1H NMR** (500 MHz, CDCl_3) δ 7.66 (d, J = 9.0 Hz, 2H), 7.40-7.38 (m, 2H), 7.34-

7.31 (m, 1H), 4.27-4.23 (m, 1H), 3.81 (s, 3H), 3.71 (s, 1H), 1.81 (d, $J = 7.5$ Hz, 1H), 1.57-1.59 (m, 2H), 1.44-1.38 (m, 1H), 1.33-1.29 (m, 1H), 0.94 (t, $J = 8.0, 8.0$ Hz, 3H). Spectral data matched those previously reported.⁷⁸

5.4 Experimental Procedures for the NHC-Catalyzed Ring Expansion for the Synthesis of Functionalized Lactones and Lactams

Epoxidation-Ring Closing Reactions.

Method A. A solution of the alcohol in CH_2Cl_2 (0.2 M) was cooled to 0 °C. *m*CPBA (1.2 equiv.) was added in one portion and the reaction was allowed to warm up to room temperature. Upon complete consumption of the alcohol, camphorsulfonic acid (0.25 equiv.) was added and stirred for an additional 24 hours. The reaction was quenched with saturated NaHCO_3 (aq) and extracted with CH_2Cl_2 (3 \times). The combined organic extracts were dried over MgSO_4 or Na_2SO_4 , then concentrated under reduced pressure. The resulting residue was purified by column chromatography.

Method B. A solution of the alcohol in CH_2Cl_2 (0.2 M) was cooled to 0 °C. *m*CPBA (1.2 equiv.) was added in one portion, opened to the air atmosphere and the reaction was allowed to warm up to room temperature, stirred for 48 hours. The reaction was quenched with saturated NH_4Cl (aq) and extracted with CH_2Cl_2 . The combined organic extracts were dried over MgSO_4 or Na_2SO_4 and then concentrated under reduced pressure. The resulting residue was purified by column chromatography.

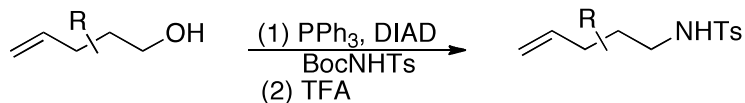
Oxidation reactions.

2-Iodoxybenzoic acid (IBX) oxidation. A suspension of the allylic or homoallylic alcohol and IBX (1.4 equiv.) in CH_3CN (0.2 M) was refluxed until complete consumption of the alcohol. The mixture was cooled to room temperature then filtered through a pad of basic alumina or Celite, washing with ethyl acetate. The filtrate was collected and concentrated under reduced pressure.

Swern oxidation. A solution of oxalyl chloride (1.1 equiv.) in dry CH_2Cl_2 (0.2 M) was cooled to $-78\text{ }^\circ\text{C}$, under inert atmosphere. DMSO (2.2 equiv.) was added to the reaction mixture, followed by the alcohol (1 equiv.) and the reaction was stirred for 30 minutes at $-78\text{ }^\circ\text{C}$. Et_3N (5 equiv.) was added dropwise and the reaction was allowed to warm up to room temperature. After complete consumption of the alcohol, the reaction was quenched with distilled water, stirred for 5 minutes and the reaction mixture was extracted CH_2Cl_2 . The combined organic extracts were dried over Na_2SO_4 , then concentrated under reduced pressure.

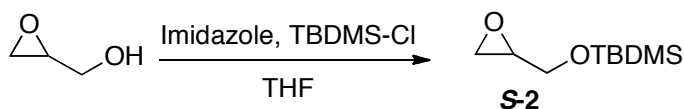
Dess-Martin Periodinane (DMP) oxidation. To a solution of the appropriate alcohol in CH_2Cl_2 , cooled to $0\text{ }^\circ\text{C}$, DMP was added. The reaction was allowed to warm up to room temperature. After the reaction is complete, the reaction mixture was diluted with CH_2Cl_2 and washed several times with a mixture of saturated $\text{NaHCO}_{3(\text{aq})}$ and saturated $\text{Na}_2\text{S}_2\text{O}_{3(\text{aq})}$. The resulting organic extract was dried over MgSO_4 or NaSO_4 then concentrated under reduced pressure.

Mitsunobu and Boc-deprotection¹¹⁷



Diisopropyl azodicarboxylate, DIAD (1.3 equiv.) was slowly added to a solution of triphenylphosphine (2 equiv.), BocNHTs (1.3 equiv.), and the corresponding alcohol substrate (1 equiv.) in dry THF (0.3 M) at room temperature. The reaction flask was then covered with aluminum foil and stirred overnight. The resulting reaction mixture was concentrated under reduced pressure, diluted with CH₂Cl₂ (0.3 M), trifluoroacetic acid (0.6 M) was slowly added. After the consumption of the starting material monitored by TLC, the reaction was quenched by slow addition of sat. NaHCO₃ (aq), then extracted with CH₂Cl₂. The combined organic extracts were dried over Na₂SO₄, concentrated, then purified by chromatography.

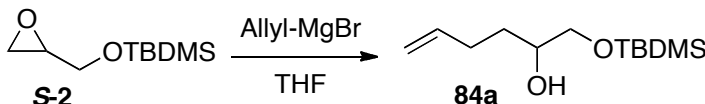
Tert-butyldimethylsilyl glycidyl ether (**S-2**)



Imidazole (1.20 g, 17.5 mmol) was added to (±)-glycidol (895 mL, 13.5 mmol) in dry THF (120 mL) at 0 °C, under nitrogen. *tert*-Butyldimethylsilyl chloride (2.60 g, 17.5 mmol) in THF (5 mL) was slowly added and the reaction mixture was allowed to warm up to room temperature and stirred for 24 hours. The reaction mixture was washed with sat. NaHCO₃ (100 mL) then brine (100 mL). The resulting organic extract was dried over MgSO₄ then concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (40% ethyl acetate in hexanes, *R_f* = 0.30), to yield a colourless oil (2.25 g, 90% yield). ¹H NMR (500 MHz, CDCl₃) δ 3.84 (dd, *J* = 11.6, 3.2

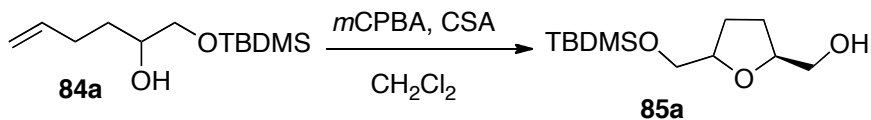
Hz, 1H), 3.66 (dd, $J = 12.6, 3.4$ Hz, 1H), 3.10-3.07 (m, 1H), 2.77 (dd, $J = 4.0, 4.0$ Hz, 1H), 2.64-2.3 (m, 1H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). Spectral data matched those previously reported.¹¹⁸

1-(*Tert*-butyldimethylsilyloxy)hex-5-en-2-ol (84a)



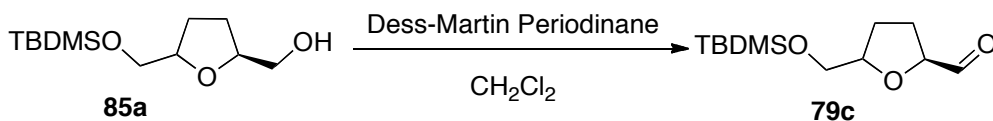
Synthesized as described by Wolfe et al.¹¹⁹ A solution of TBDMS-protected-glycidol (1.01 g, 5.37 mmol) dissolved in anhydrous THF (36 mL, 0.15 M) was cooled to 0 °C, under inert atmosphere. Allyl magnesium bromide (10.7 mL, 10.7 mmol, 1 M in Et₂O) was added dropwise, the resulting reaction mixture was warmed up rt over 2 h, then quenched with sat. NH₄Cl(aq) (15 mL). Organic layer was separated, the aqueous layer was extracted with Et₂O (3 × 15 mL), the combined organic extracts was dried over MgSO₄, then concentrated under reduced pressure. The crude product was purified by column chromatography (100% dichloromethane, $R_f = 0.30$) to yield the pure product as a colourless oil (1.00 g, 83% yield). **FTIR** (KBr film) ν_{\max} (cm⁻¹): 3443, 3079, 2955, 2930, 2858; **¹H NMR** (500 MHz, CDCl₃) δ 5.87-5.81 (m, 1H), 5.04 (d, $J = 17.1$ Hz, 1H), 4.97 (d, $J = 10.2$ Hz, 1H), 3.66-3.62 (m, 2H), 3.43 (dd, $J = 9.0, 7.5$ Hz, 1H), 2.33 (d, $J = 3.0$, 1H), 2.27-2.20 (m, 1H), 2.18-2.10 (m, 1H), 1.59-1.46 (m, 2H), 0.92 (s, 9H), 0.08 (s, 6H); **¹³C NMR** (125 MHz, CDCl₃) δ 138.5, 114.9, 71.4, 67.4, 32.2, 30.0, 26.0, 18.4, -5.2; **HRMS** (CI⁺/NH₃) m/z calcd. for C₁₂H₂₆O₂Si [M+NH₄]⁺: 248.2044, found: 248.2046.

4-(2'-*tert*-Butyl-dimethylsilyloxymethyl)tetrahydrofurfuryl alcohol (**85a**)



Epoxidation-cyclization of alkenol **84a** (487 mg, 2.12 mmol) with *m*CPBA (876 mg, 2.54 mmol, 50% in water, w/w) was performed as described in method B. The resulting residue was purified by column chromatography (4% methanol in dichloromethane, $R_f = 0.39$) to yield a colourless oil (399 mg, 76% yield, 1.5:1 dr). **FTIR** (KBr film) ν_{max} (cm^{-1}): 3496, 2959, 2927, 2855; **^1H NMR** (500 MHz, CDCl_3) δ for major isomer 4.11-4.05 (m, 2H), 3.79-3.74 (m, 2H), 3.60 (dd, $J = 19.7, 3.1$ Hz, 1H), 3.50-3.46 (m, 1H), 2.71 (br s, 1H), 1.95-1.87 (m, 4H), 0.90 (s, 9H), 0.07 (s, 6H); **^{13}C NMR** (125 MHz, CDCl_3) δ for major isomer 80.3, 80.1, 65.8, 65.6, 27.8, 27.7, 26.1, 26.1, 18.7, -5.1, -5.2, -5.3; **HRMS** (CI^+/NH_3) m/z calcd. for $\text{C}_{12}\text{H}_{26}\text{O}_3\text{Si}$ $[\text{M}+\text{NH}_4]^+$: 247.1733, found: 247.1729.

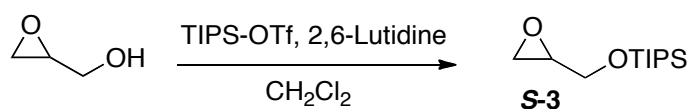
4-(2'-*tert*-Butyl-dimethylsilyloxymethyl)tetrahydrofurfuryl aldehyde (**79c**)



4-(2'-*tert*-Butyl-dimethylsilyloxymethyl)tetrahydrofurfuryl alcohol **85a** (117 mg, 0.475 mmol) was oxidized using the Dess-Martin periodinane (242 mg, 0.570 mmol) general method. The reaction gave rise to pure aldehyde **79d**, no purification was required (103 mg, 89% yield, 1.5:1 dr). **FTIR** (KBr film) ν_{max} (cm^{-1}): 2957, 2857, 1255 cm^{-1} ; **^1H NMR** (500 MHz, CDCl_3) δ 9.66 (dd, $J = 1.7, 1.7$ Hz, 1H, both epimers), 4.35-4.32 (m, 1H, one epimer), 4.24 (dddd, $J = 7.8, 7.8, 1.5, 1.5$ Hz, 1H, one epimer), 4.21-4.17 (m, 1H, both epimers), 3.71 (dddd, $J = 11.1, 11.1, 4.4, 4.4$ Hz, 1H, one epimer) 3.69-3.53 (m, 2H, both

epimers), 2.21-2.10 (m, 1H, one epimer), 2.11-2.02 (m, 1H, one epimer), 1.98-1.61 (m, 12H, epimer), 0.89 (s, 9H, both epimers), 0.88 (s, 9H, both epimers), **¹³C NMR** (125 MHz, CDCl₃) δ 204.0, 203.1, 83.7, 83.6, 81.7, 81.5, 67.7, 65.6, 28.2, 27.6, 27.5, 27.4, 26.1, 26.1, 18.5, -5.14, -5.17, -5.23; **HRMS** (CI⁺/NH₃) *m/z* calcd. for C₁₂H₂₈NO₃Si [M+NH₄]⁺: 262.1838; found: 262.1827.

3-Triisopropylsilyloxy-1,2-epoxypropane (**S-3**)



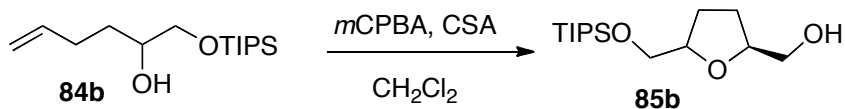
(±)-Glycidol (306 μL, 4.65 mmol) in dry CH₂Cl₂ (23 mL) was cooled to 0 °C. 2,6-Lutidine (2.0 mL, 18.6 mmol) was added, followed by triisopropylsilyl trifluoromethanesulfonate (1.5 mL, 5.6 mmol). The reaction was stirred at room temperature for 15 hours. The reaction was quenched with saturated NaHCO₃ aqueous solution (10 mL) and then extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were washed with brine, dried over MgSO₄ then concentrated under reduced pressure. The crude was purified by column chromatography (20% diethyl ether in hexanes, R_f = 0.30) to yield a colourless oil (861 mg, 80% yield). **FTIR** (KBr film) ν_{max} (cm⁻¹): 2943, 2876, 1464; **¹H NMR** (500 MHz, CDCl₃) δ 3.91 (dd, *J* = 11.7, 3.2 Hz, 1H), 3.75 (dd, *J* = 11.7, 4.7 Hz, 1H), 3.13-3.09 (m, 1H), 2.77 (dd, *J* = 4.9, 4.9 Hz, 1H), 2.69-2.65 (m, 1H), 1.56 (s, 1H), 1.14-1.08 (m, 3H), 1.07 (d, *J* = 5.6 Hz, 18H); **¹³C NMR** (125 MHz, CDCl₃) δ 64.1, 52.8, 44.6, 18.1, 12.1; **HRMS** (EI⁺) *m/z* calcd. for C₁₂H₂₆O₂Si [M]⁺: 230.1158; found 230.1148.

1-(Triisopropylsilyloxy)hex-5-en-2-ol (**84b**)



Synthesized as described by Wolfe et al.¹¹⁹ Allyl-MgBr (7.0 mL of a 1.0 M solution in Et₂O, 7.0 mmol) was added dropwise to a solution of (±)-3-triisopropylsilyloxy-1,2-epoxypropane (806 mg, 3.5 mmol) in dry THF (23 mL) at 0 °C, under inert atmosphere. The reaction was warmed up to room temperature and stirred for 2 h. The reaction was quenched with sat. NH₄Cl aqueous solution (10 mL) and extracted with Et₂O (3 × 20 mL), the organic extracts were combined, dried over MgSO₄ then concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (100 % dichloromethane, R_f = 0.30) to yield a colourless oil (741 mg, 78% yield). **FTIR** (KBr film) ν_{\max} (cm⁻¹): 3580, 3447, 2943, 2867; **¹H NMR** (500 MHz, CDCl₃) δ 5.85-5.80 (m, 1H), 5.03 (d, *J* = 17.1 Hz, 1H), 4.96 (d, *J* = 10.1 Hz, 1H), 3.72-3.66 (m, 2H), 3.49 (dd, *J* = 7.8, 7.8 Hz, 1H), 3.49 (dd, *J* = 7.9, 7.9 Hz, 1H), 2.24-2.21 (m, 1H), 2.15-2.11 (m, 1H), 1.56-1.48 (m, 2H), 1.14-1.10 (m, 3H), 1.14-1.09 (m, 3H), 1.06 (d, *J* = 6.1 Hz, 18H); **¹³C NMR** (125 MHz, CDCl₃) δ 138.6, 114.9, 71.6, 67.7, 32.2, 30.0, 18.2, 12.1, 12.1; **HRMS** (EI⁺) *m/z* calcd. for C₁₂H₂₅O₂Si [M - CH(CH₃)₂]⁺: 229.1624, found: 229.1621.

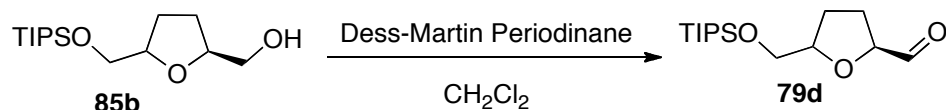
4-(2'-Triisopropylsilyloxymethyl)tetrahydrofurfuryl alcohol (**85b**)



The reaction of 1-(triisopropylsilyloxy)hex-5-en-2-ol **84b** (507 mg, 1.86 mmol) with

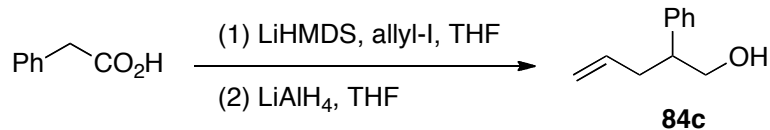
*m*CPBA (771mg, 2.23 mmol, 50% in water, w/w) was performed by following general procedure A. The reaction produced a colourless oil that require no further purification (281 mg, 52% yield). **FTIR** (KBr film) ν_{\max} (cm⁻¹): 3446, 2943, 2866, 1464, 1383; **¹H NMR** (500 MHz, CDCl₃) (3:1 dr) δ for major isomer 4.24-4.09 (m, 2H), 3.73 (ddd, *J* = 10.4, 4.2, 4.2, 2H), 3.66-3.63 (m, 1H), 3.49-3.47 (m, 1H), 2.01-1.93 (m, 4H), 1.13-1.06 (m, 21H) for minor isomer 4.24-4.09 (m, 2H), 3.73 (ddd, *J* = 13.0, 9.0, 4.0, 2H), 3.66-3.63 (m, 1H), 3.49-3.47 (m, 1H), 2.01-1.93 (m, 2H), 1.71-1.67 (m, 2H), 1.13-1.06 (m, 21H); **¹³C NMR** (125 MHz, CDCl₃) δ 80.4, 80.1, 80.0, 77.5, 77.2, 77.0, 28.4, 27.7, 27.7, 27.6, 18.0, 12.; **HRMS** (EI⁺) *m/z* calcd. for C₁₅H₃₂O₃Si [M - CH₂OH]⁺: 257.1953, found: 257.1937.

4-(2'-triisopropylsilyloxymethyl)tetrahydrofurfuryl carboxaldehyde (79d)



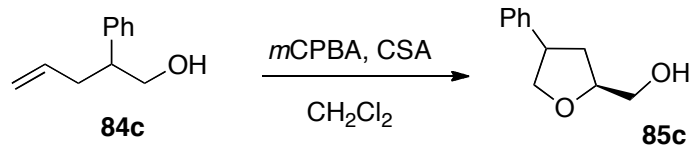
4-(2'-Triisopropylsilyloxymethyl)tetrahydrofurfuryl alcohol **85b** (105 mg, 0.364 mmol) was oxidized using Dess-Martin periodinane (105 mg, 0.364 mmol) by following the general procedure. The reaction gave rise to pure aldehyde, no purification was required (84 mg, 81% yield, 1:1 dr). **FTIR** (KBr film) ν_{\max} (cm⁻¹): 2967, 2944, 2866, 1736, 1464; **¹H NMR** (500 MHz, CDCl₃) δ 9.70 (s, 1H), 9.67 (s, 1H), 4.35-4.34 (m, 1H), 4.30-4.19 (m, 4H), 4.10-4.09 (m, 1H), 3.79-3.64 (m, 4H), 2.21-2.12 (m, 2H), 2.08-1.93 (m, 4H), 1.07 (s, 9H), 1.05 (s, 9H); **¹³C NMR** (125 MHz, CDCl₃) δ 204.0, 203.2, 83.7, 83.6, 81.9, 81.6, 65.9, 65.8, 28.3, 27.6, 27.5, 18.2, 18.2, 18.2, 12.2; **HRMS** (CI⁺) *m/z* calcd. for C₁₅H₃₀O₃Si [M]⁺: 286.1964, found: 286.2102.

2-Phenylpent-4-en-1-ol (84c)



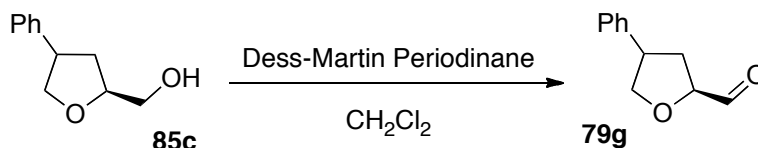
LiHMDS (8.1 mL, 8.08 mmol, 1.0 M in THF) was added to phenylacetic acid (500 mg, 3.67 mmol) in anhydrous THF (12 mL, 0.3 M) at -78 °C, under inert atmosphere. The reaction was kept at the same temperature for 30 min, then allyl-iodide (555 μ L, 6.06 mmol) was added. The reaction was warmed up to rt over 3 h, quenched with distilled water (5 mL), and then acidified to pH 4 with HCl (12.1 M). The organic layer was then removed, and the resulting aqueous layer was extracted with EtOAc (3 \times 10 mL), the combined organic extracts was washed with brine, dried over Na₂SO₄, then concentrated under reduced pressure. The crude product was then dissolved with anhydrous THF (5 mL) cooled to 0 °C, under inert atmosphere. LiAlH₄ (150 mg, 3.67 mmol) was added in 3 portions at 0 °C. After complete consumption of the starting material was observed by TLC, the reaction was quenched with ice water, then H₂SO₄ (5 M) was added until all of the alumina salts dissolves in the aqueous layer. The organic layer was removed, and the resulting aqueous was extracted with Et₂O (3 \times 10 mL), the combined organic extracts was dried over MgSO₄, and then concentrated under reduced pressure. The crude product was purified by column chromatography (20% ethyl acetate in hexanes, *R_f* = 0.30) to yield the product as a yellow oil (371 mg, 62% yield, 1:1 dr). **¹H NMR** (500 MHz, CDCl₃) δ 7.35-7.32 (m, 3H), 7.24-7.22 (m, 2H), 5.78-5.70 (m, 1H), 5.11-4.96 (m, 1H), 3.84-3.65 (m, 2H), 2.93-2.81 (m, 1H), 2.57-2.47 (m, 1H), 2.44-2.38 (m, 1H). Spectral data matched those previously reported.¹²⁰

(4-phenyl-tetrahydrofuran-2-yl)methanol (**85c**)



Epoxidation-cyclization of alkenol **84c** (60 mg, 0.370 mmol) with *m*CPBA (153 mg, 0.444, mmol, 50% in water, w/w) and CSA (40 mg) was performed as described in method A. The resulting residue was purified by column chromatography (50% ethyl acetate in hexanes, R_f = 0.30) to yield a colourless oil (41 mg, 62% yield, 1.3:1 dr). **¹H NMR** (500 MHz, CDCl₃) δ 7.34-7.31 (m, 4H), 7.26-7.22 (m, 6H), 4.35-4.30 (m, 1H), 4.28-4.20 (m, 2H), 3.83-3.74 (m, 2H), 3.65 (dd, J = 12.4, 6.1 Hz, 1H), 3.59 (dd, J = 11.4, 5.7 Hz, 1H), 3.55-3.42 (m, 2H), 2.37 (dddd, J = 11.8, 6.5, 6.5, 6.5 Hz, 1H), 2.21 (dddd, J = 13.4, 13.4, 9.3, 5.9 Hz, 1H), 2.12-2.05 (m, 2H), 1.93-1.86 (m, 1H), missing 2H's. Spectral data matched those previously reported.¹²¹

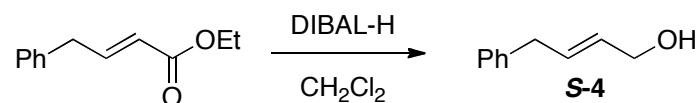
4-Phenyl-tetrahydrofuran-2-carbaldehyde (**79g**)



Alcohol **85c** (90 mg, 0.506 mmol) was oxidized using Dess-Martin periodinane (257 mg, 0.607 mmol) by following the general procedure. The reaction gave rise to pure aldehyde as a colourless oil, no purification was required (43 mg, 48% yield, 2.5:1 dr). **FTIR** (KBr film) ν_{\max} (cm⁻¹): 3062, 3028, 2925, 2851, 1733, 1603, 1495, 1456, 1261; **¹H NMR** (500 MHz, CDCl₃) δ 9.80 (s, 1H, major epimer), 9.77 (s, 1H, minor epimer), 7.36-7.33 (m, 5H, both epimers), 7.28-7.23 (m, 5H, both epimers), 4.55 (dd, J = 9.0, 4.3 Hz, 1H,

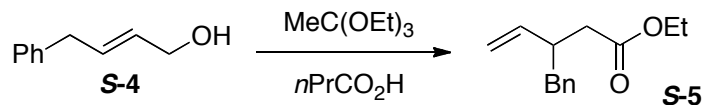
major epimer), 4.46 (dd, $J = 8.0, 8.0$ Hz, 1H, minor epimer), 4.38-4.32 (m, 2H, both epimers), 3.95 (dd, $J = 8.1, 8.1$ Hz, 1H, major epimer), 3.89 (dd, $J = 8.9, 8.9$ Hz, 1H, minor epimer), 3.57-3.48 (m, 1H, minor epimer), 3.39 (dddd, $J = 15.4, 15.4, 8.0, 8.0$ Hz, 1H, major epimer), 2.65 (dddd, $J = 15.6, 12.6, 7.6, 7.6$ Hz, 1H, minor epimer), 2.54 (dddd, $J = 12.6, 12.6, 7.8, 4.0$ Hz, 1H, major epimer), 2.29 (ddd, $J = 17.2, 12.2, 8.2$ Hz, 1H, major epimer), 2.15-2.05 (m, 1H, minor epimer); ^{13}C NMR (500 MHz, CDCl_3) δ 202.7, 202.2, 140.8, 139.9, 128.9, 128.9, 128.8, 127.4, 127.3, 127.2, 83.4, 83.3, 75.5, 75.4, 45.0, 44.3, 35.7, 35.6. HRMS (EI^+) m/z calcd. for $\text{C}_{11}\text{H}_{12}\text{O}_2$ $[\text{M}]^+$: 176.0837, found: 176.0833.

(2E)-4-Phenylbut-2-en-1-ol (S-4)



Diisopropylaluminium hydride (12.0 mL of a 1.0 M solution in hexane, 12.0 mmol) was added to a solution of the ester in dry CH_2Cl_2 (18 mL) at 0 °C under inert atmosphere. The mixture was stirred at 0 °C for 45 min, then warmed up to room temperature for 30 minutes. The mixture was quenched with 2 M HCl (aq) (20 mL) at 0 °C and extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were dried over Na_2SO_4 , then concentrated under reduced pressure to yield the alcohol as a colorless oil (794 mg, 76% yield), no purification was required. ^1H NMR (500 MHz, CDCl_3) δ 7.31-7.28 (m, 2H), 7.22-7.18 (m, 3H), 5.88-5.84 (m, 1H), 5.74-5.59 (m, 1H), 4.13 (d, $J = 5.8$ Hz, 2H), 3.39 (d, $J = 6.7$ Hz, 2H). Spectral data matched those previously reported.¹²²

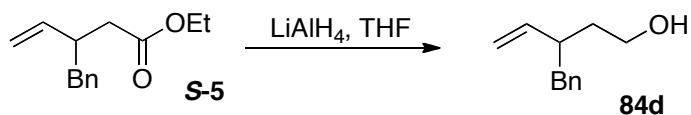
Ethyl-3-(benzyl)hex-4-enoate (**S-5**)



A solution of the alcohol (794 mg, 5.36 mmol), triethylorthoacetate (6.5 mL, 35.4 mmol), and propanoic acid (240 μ L, 3.22 mmol) was stirred in a flask fitted with a Dean-Stark apparatus and a reflux condenser, at 150 $^{\circ}$ C for 17 h. The reaction was allowed to cool down to room temperature before diluting with Et₂O (10 mL), followed by 1 M HCl (aq) (10 mL). The two layers were separated, then the aqueous layer was extracted with Et₂O (3 \times 10 mL), the combined organic extracts were dried over Na₂SO₄ then concentrated under reduced pressure. The residue was purified by column chromatography (10% ethyl acetate in hexanes, R_f = 0.35) to yield the product as a yellow oil (816 mg, 70% yield).^{xiv}

¹H NMR (500 MHz, CDCl₃) 7.31-7.27 (m, 2H), 7.23-7.15 (m, 3H), 5.75 (dt, J = 18.1, 8.6 Hz, 1H), 4.98 (dd, J = 16.0 Hz, 12.3, 2H), 4.15-4.06 (dt, J = 14.5, 7.4 Hz, 2H), 2.90 (dt, J = 15.6, 8.6 Hz, 1H), 2.69 (d, J = 6.9 Hz, 2H), 2.72 (dd, J = 8.2, 5.9 Hz, 2H), 1.27 (dddd, J = 13.9, 7.4 Hz, 3H).

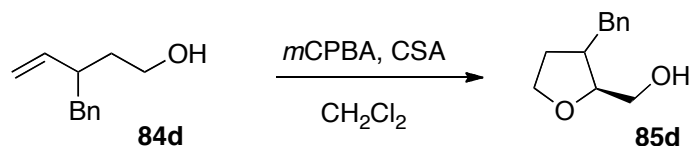
3-(Benzyl)hex-4-en-1-ol (**84d**)¹²³



Lithium aluminum hydride (148 mg, 3.69 mmol) was added in two portions to a stirring solution of ethyl-4-phenylbut-2-enoate¹²⁴ in *tert*-butyl methyl ether (5 mL) at 0 $^{\circ}$ C. The suspension was stirred for 1 h at 0 $^{\circ}$ C, then poured into ice/water (10 mL). Sulfuric acid

(5 M) was added until the aluminium salts dissolved. The two phases were separated and the aqueous layer was extracted with Et₂O (2 × 10 mL). The combined organic layers were dried over Na₂SO₄ then concentrated under reduced pressure. The residue was purified by column chromatography (33% ethyl acetate in hexanes, *R_f* = 0.37) to yield a colourless oil (353 mg, 54% yield). **FTIR** (KBr film) ν_{max} (cm⁻¹): 3337, 3064, 3027, 2928, 699; **¹H NMR** (500 MHz, CDCl₃) δ 7.32-7.29 (m, 2H), 7.23-7.18 (m, 3H), 5.68 (dddd, *J* = 17.9, 9.3 Hz, 1H), 5.00 (dd, *J* = 17.7, 11.1 Hz, 2H), 3.71 (dt, *J* = 10.7, 6.3 Hz, 1H), 3.64 (dt, *J* = 14.1, 6.7 Hz, 1H), 2.70 (d, *J* = 7.0 Hz, 1H), 2.58-2.48 (m, 1H), 1.74 (dddd, *J* = 11.8, 7.0 Hz, 1H), 1.59-1.54 (m, 1H), 1.48 (s, 1H); **¹³C NMR** (125 MHz, CDCl₃) δ 142.1, 140.3, 129.5, 128.3, 126.1, 115.4, 61.3, 42.9, 42.2, 37.0; **HRMS** (EI⁺) *m/z* calcd. for C₁₂H₁₈O [M]⁺: 176.1201, found: 176.1208.

2-Benzyl-tetrahydrofurfuryl alcohol (85d)

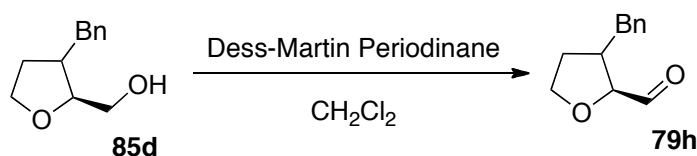


2-Benzyl-tetrahydrofurfuryl alcohol was prepared by reacting 3-(benzyl)hex-4-en-1-ol (311 mg, 1.78 mmol) with *m*CPBA (731 mg, 2.12 mmol, 50% in water, w/w), following the procedures outlined in method A. The residue was purified by column chromatography (66% ethyl acetate in hexanes, *R_f* = 0.31) to yield a colourless oil (130 mg, 38% yield, 1.5:1 dr). **FTIR** (KBr film) ν_{max} (cm⁻¹): 3425, 3026, 2936; **¹H NMR** (500 MHz, CDCl₃) δ 7.32-7.28 (m, 2H, two epimers), 7.22-7.17 (m, 3H, two epimers), 4.01

^{xiv} The purity of the desired product was 75%, contaminated with the starting material. When the reaction time is increased to 24 h, decomposition is observed.

(ddd, $J = 6.8, 6.8, 3.9$ Hz, 1H, major epimer), 3.96 (ddd, $J = 8.3, 8.3, 3.6$ Hz, 1H, major epimer), 3.84 (ddd, $J = 14.9, 14.9, 7.5$ Hz, 1H, minor epimer), 3.77 (ddd, $J = 7.5, 7.5, 7.5$ Hz, 1H, minor epimer), 3.70 (ddd, $J = 8.6, 8.6, 7.1$ Hz, 1H, major epimer), 3.64 (ddd, $J = 6.4, 6.4, 3.0$ Hz, 1H, minor epimers), 3.63-3.58 (m, 2H, two epimers), 3.49 (dd, $J = 11.8, 3.0$ Hz, 1H, minor epimer), 3.34 (dd, $J = 11.8, 5.8$ Hz, 1H, major epimer), 2.78 (dd, $J = 12.6, 4.3$ Hz, 1H, major epimer), 2.70 (dd, $J = 13.5, 6.8$ Hz, 1H, minor epimer), 2.62 (dd, $J = 13.5, 8.1$ Hz, 1H, minor epimer), 2.59-2.54 (m, 2H, two epimers), 2.24 (ddd, $J = 15.6, 15.6, 7.9$ Hz, 1H, minor diastereomer), 1.96 (dddd, $J = 15.0, 15.0, 7.3, 7.3$ Hz, 1H, minor epimer), 1.8-1.82 (m, 1H, major epimer), 1.70-1.61 (m, 2H, two epimers); ^{13}C NMR (125 MHz, CDCl_3) δ 140.8, 140.3, 128.9, 128.8, 128.7, 128.6, 128.4, 128.3, 84.7, 90.0, 67.6, 67.3, 64.0, 62.6, 62.6, 42.6, 41.9, 39.3, 34.9, 33.0, 31.9; HRMS (EI^+) m/z calcd. for $\text{C}_{12}\text{H}_{16}\text{O}_2$ $[\text{M}]^+$: 192.1150, found: 192.1131.

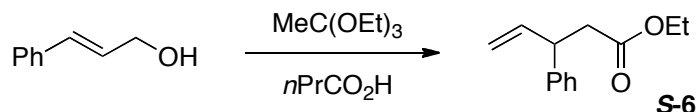
2-Benzyl-tetrahydrofurfuryl aldehyde (79h)



Dess-Martin periodinane (122 mg, 0.288 mmol) was added to a solution of oxacycloalkane alcohol (46 mg, 0.240 mmol) in CH_2Cl_2 (1 mL) at 0 °C. The reaction was stirred at room temperature for 2 h. The resulting reaction mixture was diluted with CH_2Cl_2 (10 mL), and then washed with (1:1, v/v, 3×20 mL) sat. NaHCO_3 (aq) and sat. $\text{Na}_2\text{S}_2\text{O}_3$ (aq). The resulting organic layer was dried over NaSO_4 , and then concentrated under reduced pressure to yield a colourless oil. The reaction gave rise to pure aldehyde **79h**, no purification was required (27 mg, 59% yield, 1.5:1 dr). FTIR (KBr film) ν_{max}

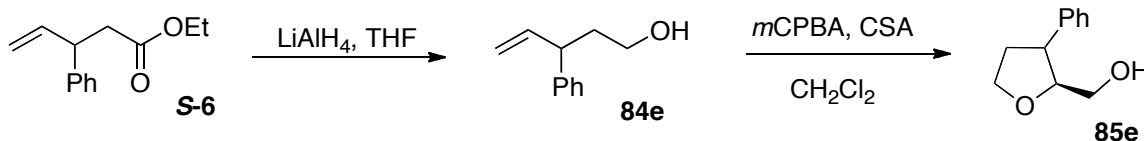
(cm^{-1}): 3027, 2940, 1730, 1496, 1454; **^1H NMR** (500 MHz, CDCl_3) δ 9.79 (d, $J = 2.0$ Hz, 1H, one epimer), 9.57 (d, $J = 1.5$ Hz, 1H, one epimer), 7.34-7.31 (m, 4H, both epimers), 7.24-7.20 (m, 6H, both epimers), 4.35 (dd, $J = 7.6, 1.8$ Hz, 1H, one epimer), 4.23-4.22 (m, 1H, one epimer), 4.09-4.05 (m, 1H, one epimer), 4.00-3.99 (m, 1H, one epimer), 3.96-3.90 (m, 2H, both epimers), 2.97-2.86 (m, 3H, both epimers), 2.73 (dd, $J = 13.5, 8.5$ Hz, 1H, one epimer), 2.63-2.56 (dddd, $J = 14.0, 14.0, 7.0, 7.0$ Hz, 1H, one epimer), 2.51-2.46 (m, 1H, one epimer), 2.06-1.98 (m, 2H, one epimer), 1.80-1.71 (m, 2H, one epimer); **^{13}C NMR** (125 MHz, CDCl_3) δ 203.2, 202.2, 139.9, 139.5, 129.0, 128.7, 128.7, 126.6, 126.6, 87.1, 85.1, 69.0, 68.6, 53.6, 44.8, 43.3, 38.7, 35.3, 31.9, 31.6; **HRMS** (Cl^+) m/z calcd. for $\text{C}_{12}\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{NH}_4]^+$: 208.1338, found: 208.1332.

Ethyl 2-phenylbut-3-enoate (**S-6**)



Ester **S-6** was synthesized using the same procedure for the synthesis of **S-6**. Colourless oil (701 mg, 92% yield). $R_f = 0.30$ (10% ethyl acetate in hexanes). **^1H NMR** (500 MHz, CDCl_3) δ 7.32-7.29 (m, 2H), 7.22-7.20 (m, 3H), 6.02-5.95 (m, 1H), 5.07 (dd, $J = 13.9, 4.0$ Hz, 2H), 4.07 (q, $J = 6.9, 6.9, 6.9, 6.9$ Hz, 2H), 2.81-2.67 (m, 2H), 1.17 (t, $J = 7.6, 7.6$ Hz, 3H). Spectral data matched those previously reported.¹²⁵

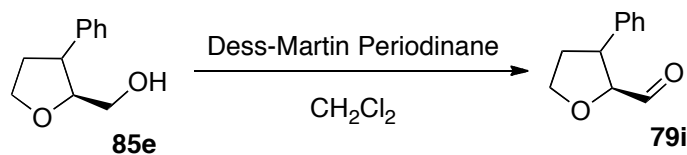
(3-Phenyl-tetrahydrofuran-2-yl)methanol (85e)



Ester **S-6** (267 mg, 1.31 mmol) was dissolved in *tert*-butyldimethylether (2 mL, 0.7 M) under inert atmosphere. The solution was cooled to 0 °C, then LiAlH_4 (52 mg, 1.31 mmol) was added, the reaction mixture was allow to warm up to rt over 24 h. The reaction mixture was then poured into ice-water, H_2SO_4 (5 M) was added until alumina salts dissolved, the two phases were separated. The resulting aqueous layer was extracted with Et_2O (3×5 mL), the combined organic extracts was dried over MgSO_4 , then concentrated under reduced pressure. Purification of **84e** was performed with column chromatography (20% ethyl acetate in hexanes, $R_f = 0.30$) to yield the impure alcohol product. The alcohol was then dissolved in CH_2Cl_2 (4 mL), cooled to 0 °C. $m\text{CPBA}$ (304 mg, 0.882 mmol, 50% in water, w/w) was added. After the addition, the reaction was allowed to warm up to rt over 24 h. CSA (50 mg) was added and stirred for an additional 24 h. The reaction was quenched with sat. NH_4Cl (aq) (5 mL), sat. $\text{Na}_2\text{S}_2\text{O}_3$ (5 mL) was then added. The organic layer was washed with sat. sat. NH_4Cl (aq) (3×5 mL), sat. $\text{Na}_2\text{S}_2\text{O}_3$ (3×5 mL), dried over MgSO_4 , then concentrated under reduced pressure. The crude product was purified by column chromatography (4% methanol in dichloromethane, $R_f = 0.30$) to yield the product as a yellow oil (42 mg, 18% over 2 steps, 1:1 dr). **^1H NMR** (500 MHz, CDCl_3) δ 7.37-7.23 (m, 10H), 4.27-4.19 (m, 2H), 4.15 (dddd, $J = 8.6, 8.6, 8.6, 4.4$ Hz, 1H), 4.04 (dddd, $J = 8.3, 8.3, 8.3, 8.3$ Hz, 1H), 3.99-3.94 (m, 2H), 3.78-3.76 (m, 1H), 3.58-3.52 (m, 2H), 3.26-3.20 (m, 3H), 2.45-2.36 (m, 2H), 2.32-2.26 (m, 1H), 2.25-2.17 (m, 1H). Spectral data matched those previously

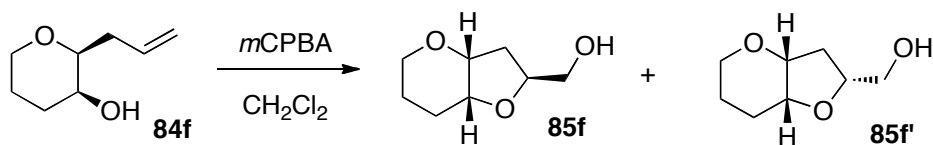
reported.¹²¹

3-Phenyl-tetrahydrofuran-2-carbaldehyde (79i)



Alcohol **85e** (28 mg, 0.158 mmol) was oxidized using Dess-Martin periodinane (81 mg, 0.190 mmol) by following the general procedure. The reaction gave rise to impure aldehyde as a colourless oil (17 mg, ~61% yield, 2.6:1 dr). **FTIR** (KBr film) ν_{max} (cm⁻¹): 3028, 2976, 1730, 1680, 1657, 1603, 1563, 1555, 1511, 1494, 1453; **¹H NMR** (500 MHz, CDCl₃) δ 9.74 (d, J = 1.6 Hz, 1H, minor epimer), 9.32 (d, J = 1.7 Hz, 1H, major epimer), 7.39-7.29 (m, 5H, both epimers), 7.27-7.20 (m, 5H, both epimers), 4.52 (dd, J = 7.7, 2.0 Hz, 1H, major epimer), 4.41 (dddd, J = 13.2, 8.3, 8.3, 4.6 Hz, 1H, major epimer), 4.35 (dd, J = 6.4, 1.7 Hz, 1H, minor epimer), 4.28-4.22 (m, 1H, minor epimer), 4.09 (dddd, J = 8.1, 8.1, 8.1, 8.1, 2H, major epimer), 3.83 (dddd, J = 7.5, 7.5, 7.5, 7.5 Hz, 2H, minor epimer), 2.52-2.45 (m, 2H, both epimers), 2.32-2.24 (m, 2H, both epimers); **HRMS** (CI⁺/NH₃) m/z calcd. for C₁₁H₁₂O₂ [M+NH₄]⁺: 194.1181, found: 194.1189.

Hexahydro-2H-furo[3,2-*b*]pyran-2-yl)methanol (85f) and (85f')



To a solution of 2-allyl-3-hydroxytetrahydropyran **84f** (582 mg, 4.10 mmol), (prepared as described by Rousseau *et al.*),¹²⁶ in CH₂Cl₂ (21 mL) was added mCPBA (1.70g, 4.92

mmol) at 0 °C. The reaction was warmed up to room temperature and stirred for 12 h. The reaction mixture was concentrated under reduced pressure. CHCl₃ (20 mL) was added and mixed well, before cooling in an ice-water bath. The precipitate, *m*-chlorobenzoic acid was filtered off by vacuum filtration. The mother filtrate was transferred to a separatory funnel and extracted with a sat. NaHCO₃ (aq) (20 mL), the aqueous layer was saturated with solid NaCl and back-extracted with CHCl₃ (3 × 20 mL). The combined organic extracts were dried over Na₂SO₄, then concentrated under reduced pressure. The residue was purified by column chromatography (4% methanol in dichloromethane, *R_f*(**85f**) = 0.22, *R_f*(**85f'**) = 0.16) to yield both isomers as colourless oils (**85f** – 258 mg, 40% yield, **85f'** – 137 mg, 21%). The relative configurations of the two isomers were determined by NOE experiments.

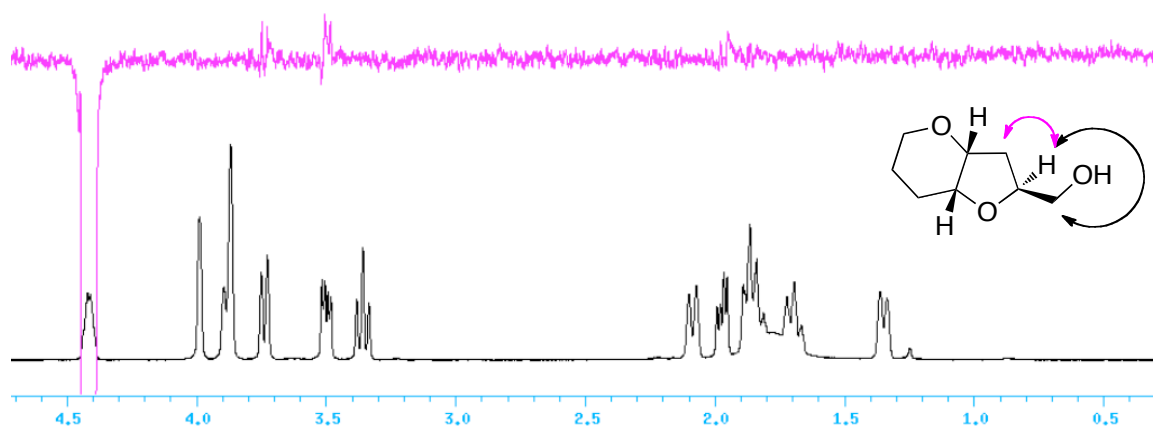
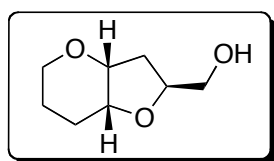


Figure 5.1 NOE Experiment for the Determination of the Relative Configuration of **85f**.



(**85f**): FTIR (KBr film) ν_{max} (cm⁻¹): 3425, 3026, 2936; ¹H NMR (500 MHz, CDCl₃) δ 4.19-4.17 (m, 1H), 3.87 (s, 2H), 3.74-3.70

(m, 2H), 3.55 (d, $J = 11.1$ Hz, 1H), 3.37-3.32 (dd, $J = 11.7, 11.7$ Hz, 1H), 3.08 (br s, 1H), 2.19-2.17 (m, 1H), 2.10-2.07 (m, 1H), 1.89-1.82 (m, 2H), 1.69-1.67 (m, 1H), 1.32-1.29 (m, 1H). ^{13}C NMR (125 MHz, CDCl_3) δ 78.2, 76.4, 76.3, 66.8, 65.2, 35.6, 25.2, 20.2; HRMS (CI^+/NH_3) m/z calcd. for $\text{C}_8\text{H}_{14}\text{O}_3$ $[\text{M}+\text{NH}_4]^+$: 176.1285, found: 176.1287.

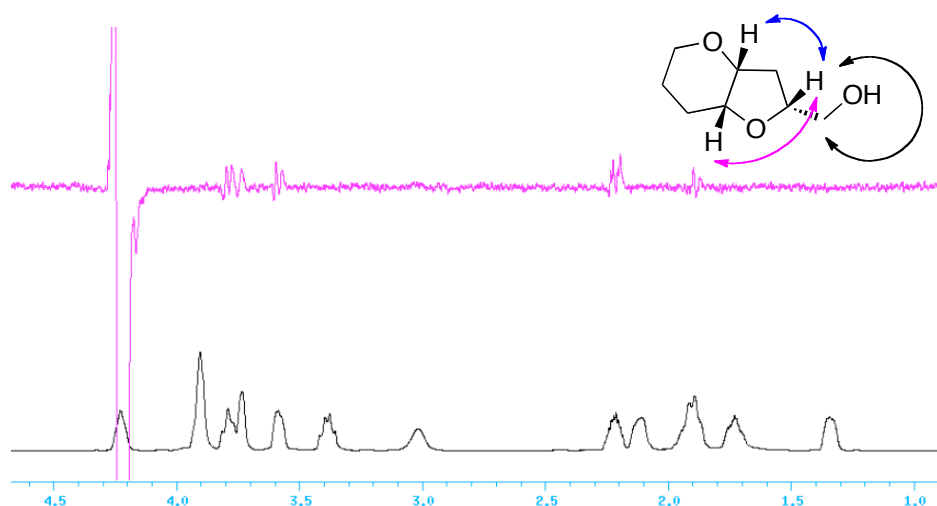
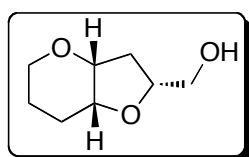
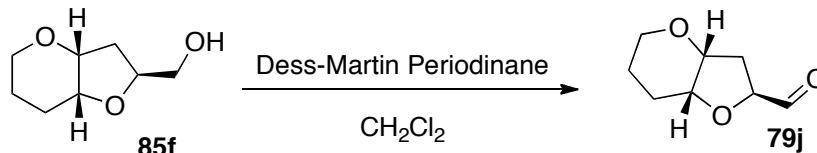


Figure 5.2 NOE Experiment for the Determination of the Relative Configuration of **85f**.



85f: FTIR (KBr film) ν_{max} (cm^{-1}): 3439, 2926, 2874; ^1H NMR (500 MHz, CDCl_3) 4.38 (d, $J = 5.4$ Hz, 1H), 3.96 (s, 1H), 3.86-3.84 (m, 2H), 3.70 (d, $J = 11.5$ Hz, 1H), 3.47 (dd, $J = 11.3, 5.3$ Hz, 1H), 3.35-3.30 (dd, $J = 11.9, 5.3$ Hz, 1H), 2.41 (s, 1H), 2.05 (d, $J = 14.3$ Hz, 1H), 1.96-1.92 (dd, $J = 13.2, 6.4$ Hz, 1H), 1.86-1.78 (m, 2H), 1.69-1.64 (dd, $J = 14.2$ Hz, 1H), 1.32 (d, 1H, $J = 11.9$ Hz). ^{13}C NMR (125 MHz, CDCl_3) δ 79.1, 77.3, 75.8, 66.5, 65.1, 35.8, 25.7, 20.3; HRMS (CI^+/NH_3) m/z calcd. for $\text{C}_8\text{H}_{14}\text{O}_3$ $[\text{M}+\text{NH}_4]^+$: 176.1283, found: 176.1287.

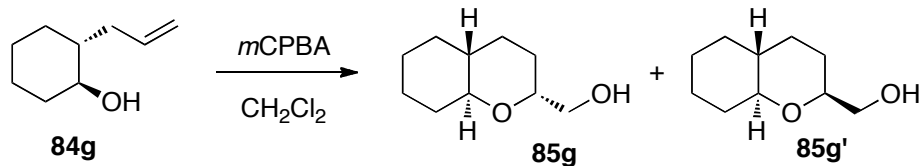
Hexahydro-2*H*-furo[3,2-*b*]pyran-2-carbaldehyde (79j**).**



Dess-Martin periodinane (209 mg, 0.729 mmol) was added to a solution of alcohol **85f** (96 mg, 0.608 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The reaction was stirred at room temperature for 3 h. The resulting reaction mixture was filtered through a fritted funnel then washed with diethyl ether. The resulting mother filtrate was concentrated under reduced pressure. Diethyl ether was added and the solution was swirled and placed in an ice-bath, the precipitate (Dess-Martin periodinane byproducts) were filtered off through a cotton pipette and washed with cold diethyl ether. The resulting solution was then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (5 mL) and quickly filtered through a pad of silica, and then concentrated under reduced pressure to yield a colorless oil (32 mg, 31 % yield).^{xv} The reaction gave rise to 90% pure aldehyde **79j** (32 mg, 31% yield).^{xvi} **FTIR** (KBr film) ν_{max} (cm^{-1}): 2954, 2916, 2848; **^1H NMR** (500 MHz, CDCl_3) δ 9.77 (s, 1H), 4.27 (d, $J = 10.2$ Hz, 1H), 3.99-3.87 (m, 3H), 3.35 (dd, $J = 12.2, 12.2$ Hz, 1H), 2.30 (dddd, $J = 10.2, 10.1, 3.6, 3.5$ Hz, 1H), 2.20 (d, $J = 13.7$ Hz, 2H), 1.96-1.89 (m, 1H), 1.79-1.72 (m, 1H), 1.38 (d, $J = 13.5$ Hz, 1H); **^{13}C NMR** (125 MHz, CDCl_3) δ 205.2, 81.5, 77.8, 75.0, 66.6, 39.0, 25.5, 20.1; **HRMS** (CI^+/NH_3) m/z calcd. for $\text{C}_8\text{H}_{16}\text{O}_3$ $[\text{M}+\text{NH}_4]^+$: 174.1130, found: 174.1126.

^{xv} Aldehyde **79j** is water soluble, therefore, the general workup method, washing with saturated aqueous solutions of $\text{Na}_2\text{S}_2\text{O}_3$ and NaHCO_3 had to be avoided; in addition, **79j** appears to be unstable to silica gel column chromatography, therefore, filtration through a small pad of silica needs to be done quickly to avoid decomposition.

***trans*-2-But-3-enylcyclohexanol (**84g**) and (**85g**)'**



Trans-2-but-3-enylcyclohexanol **84g** was synthesized as described by Hone et al.¹²⁷ Bicyclic alcohol **85g** and **85g'** was synthesized by method B, to yield the product as a colourless oil (319 mg, 55% yield, major product = **85g**); *R_f* (**85g**) = 0.50 and *R_f* (**85g'**) = 0.30 (60% ethyl acetate in hexanes).

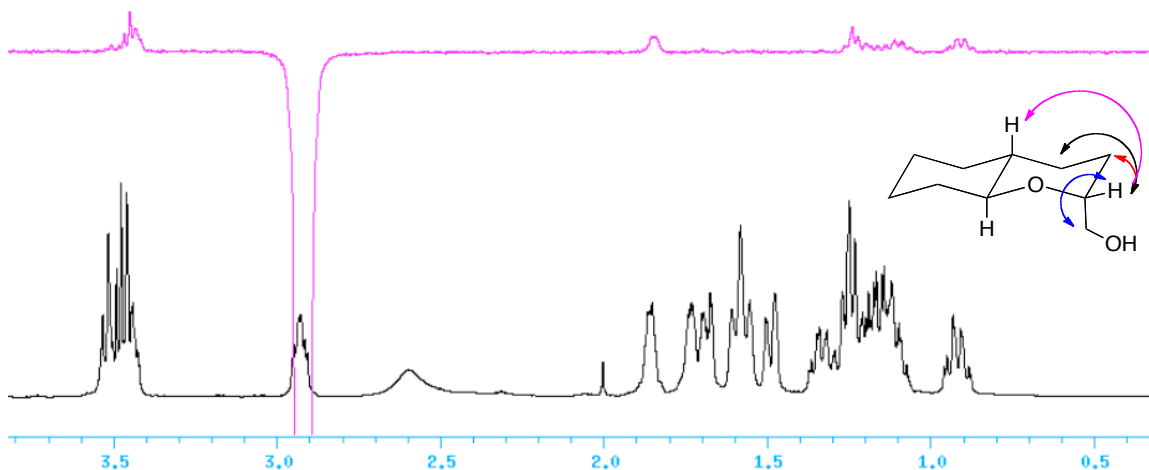
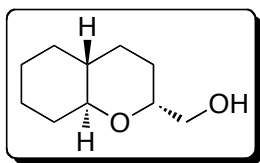


Figure 5.3 NOE Experiment for the Determination of the Relative Configuration of **85g**.



85g: FTIR (KBr film) ν_{max} (cm⁻¹): 2954, 2916, 2848; ¹H NMR (500 MHz, CDCl₃) δ 3.58-3.54 (m, 1H), 3.53-3.50 (m, 1H), 3.48-3.46 (m, 1H), 2.99-2.94 (m, 1H), 2.52-2.42 (br s, 1H), 1.92-1.87 (m, 1H), 1.80-1.75 (m, 1H), 1.75-1.69 (m, 1H), 1.62 (m, 2H), 1.55-1.50 (m, 1H), 1.42-1.33 (m, 1H), 1.31-1.27 (m, 2H), 1.25-1.11 (m, 4H), 1.00-0.92 (m, 1H); ¹³C NMR (500 MHz,

^{xvi} Purity of aldehyde was determined by NMR.

CDCl₃) δ 82.0, 78.3, 66.4, 42.0, 32.6, 31.8, 30.5, 28.0, 25.9, 25.2; **HRMS** (CI⁺/NH₃) m/z calcd. for C₁₀H₁₈O₂ [M+NH₄]⁺: 170.1307, found: 170.1291.

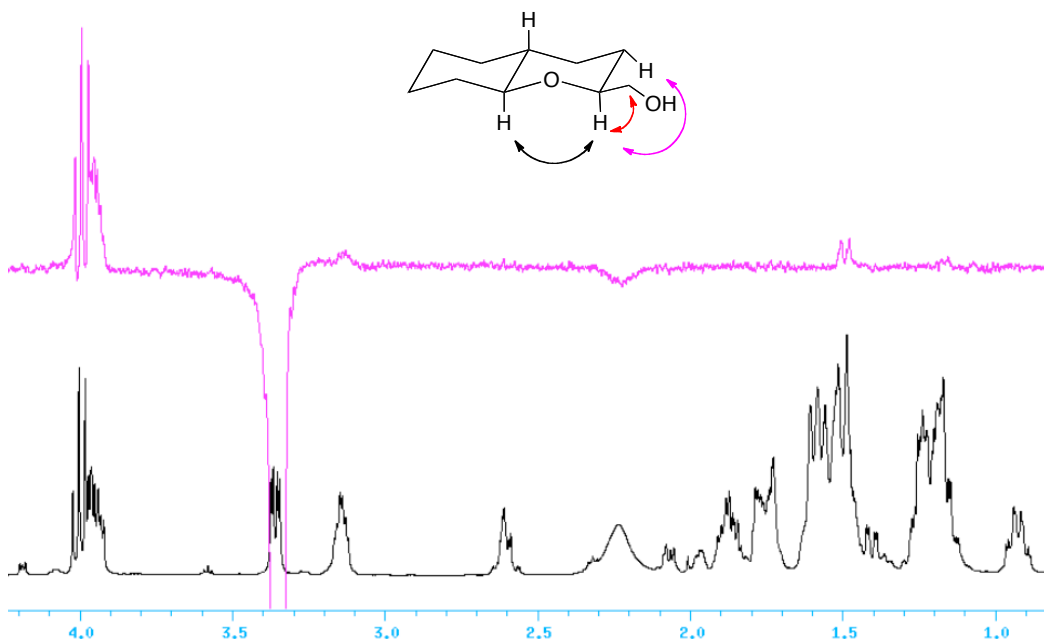
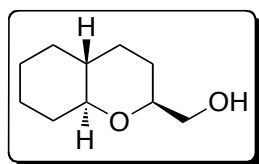
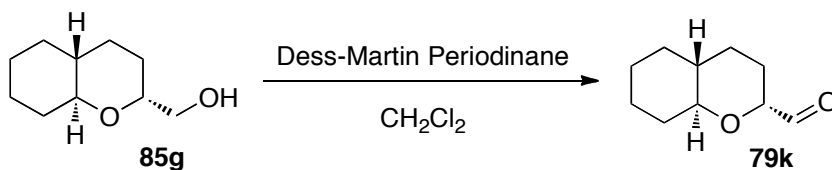


Figure 5.4 NOE Experiment for the Determination of the Relative Configuration of **85g'**.



85g': ¹H NMR (500 MHz, CDCl₃) δ 4.05-3.99 (ddd, J = 22.0, 12.0 Hz, 1H), 3.98-3.94 (m, 1H), 3.38-3.35 (dd, J = 11.0, 4.0 Hz, 1H), 3.18-3.14 (m, 1H); ¹³C NMR (500 MHz, CDCl₃) δ 82.0, 78.3, 66.4, 42.0, 32.6, 31.8, 30.5, 28.0, 25.9, 25.2.

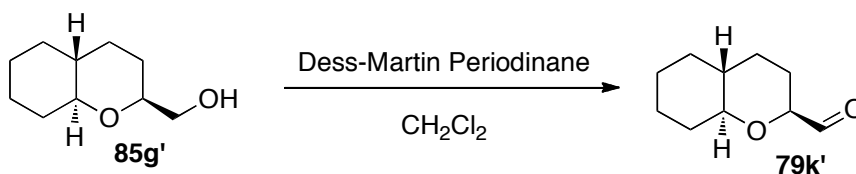
(2*R*,4*aR*,8*aS*)-Octahydro-2*H*-chromene-2-carbaldehyde (79k**)**



Alcohol **85g** was oxidized following the general procedure with Dess-Martin periodinane

to yield **79k** as a colourless oil (29 mg, 45% yield). **FTIR** (KBr film) ν_{\max} (cm⁻¹): 2929, 2861, 1740, 1230; **¹H NMR** (500 MHz, CDCl₃) δ 9.61 (s, 1H), 3.83 (d, J = 11.3 Hz, 1H), 3.03-2.99 (m, 1H), 2.02-1.78 (m, 6H), 1.65-1.60 (m, 4H), 1.28-1.20 (m, 3H); **¹³C NMR** (500 MHz, CDCl₃) δ 202.2, 82.3, 82.0, 41.6, 32.5, 31.7, 30.2, 27.0, 25.8, 25.2; **HRMS** (EI⁺) m/z calcd. for C₁₀H₁₆O₂ [M-CHO]⁺: 139.1123, found: 139.1121.

(2*S*,4*aR*,8*aS*)-Octahydro-2*H*-chromene-2-carbaldehyde (79k'**)**



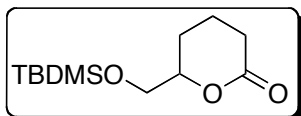
Alcohol **85g'** was oxidized following the general procedure with Dess-Martin periodinane to yield **79k'** as a colourless oil (38 mg, 69% yield). **FTIR** (KBr film) ν_{\max} (cm⁻¹): 2930, 2859, 1731, 1449, 1349, 1329; **¹H NMR** (500 MHz, CDCl₃) δ 9.87 (s, 1H), 4.19 (d, J = 5.7 Hz, 1H), 3.15-3.12 (m, 1H), 2.67-2.56 (m, 1H), 2.20-2.04 (m, 2H), 1.97-1.91 (m, 2H), 1.81-1.76 (m, 4H), 1.35-1.14 (m, 4H); **¹³C NMR** (500 MHz, CDCl₃) δ 205.9, 79.7, 79.4, 41.4, 32.8, 31.8, 27.4, 25.8, 25.1, 24.5.

General Procedure for the NHC-Catalyzed Ring Expansion Reaction to Access Functionalized Lactones.

To a 0.5 M solution of oxacycloalkane-2-carboxaldehyde (1 equiv.) in anhydrous CH₂Cl₂ was added 1,3-bis-(2,6-diisopropylphenyl)imidazolinium chloride **87b** (0.10 equiv.), followed by DBU (0.08 equiv.) under nitrogen at room temperature. The reaction was monitored by thin layer chromatography, and quenched using 10% NH₄Cl (aq). The

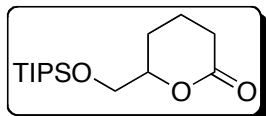
mixture was then extracted using CH₂Cl₂ (×3). The combined organic layers were dried over Na₂SO₄, concentrated under reduced pressure, and purified by column chromatography to afford the lactone.

Tetrahydro-6-*O*-(*tert*-butyldimethylsilylmethyl)-2H-pyran-2-one (83c)



Lactone **83c** was synthesized by following the general procedure, however, the reaction required 30 mol % catalyst loading of **91b**. The crude was purified by column chromatography (20% ethyl acetate in hexanes, R_f = 0.31) to yield a colourless oil (18 mg, 29% yield). **FTIR** (KBr film) ν_{\max} (cm⁻¹): 2955, 2930, 2857, 1742; **¹H NMR** (500 MHz, CDCl₃) δ 4.36-4.31 (dddd, J = 9.2, 9.2, 3.9, 3.9 Hz, 1H), 3.76 (ddd, J = 14.8, 10.8, 4.1 Hz, 1H), 3.70 (ddd, J = 16.2, 10.7, 5.4 Hz, 1H), 2.60-2.57 (ddd, J = 12.5, 12.5, 6.1 Hz, 1H), 2.47-2.42 (m, 1H), 1.97-1.92 (m, 1H), 1.73-1.69 (m, 1H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 171.5, 80.5, 65.3, 30.1, 26.0, 26.0, 24.6, 18.5, 18.5, -5.2; **HRMS** (CI⁺/NH₃) m/z calcd for C₁₂H₂₈NO₃Si [M+NH₄]⁺: 262.1838, found: 262.1833.

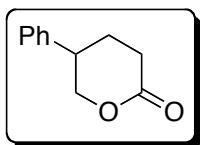
Tetrahydro-6-*O*-(triisopylsilylmethyl)-2H-pyran-2-one (83d)



Lactone **83d** was synthesized according to the general procedure as a colourless oil (22 mg, 32% yield). R_f = 0.32 (25% ethyl acetate in hexanes). **FTIR** ν_{\max} (cm⁻¹): 2944, 2866, 1742, 1464, 1240; **¹H NMR** (500 MHz, CDCl₃) δ 4.36-4.35 (m, 1H), 3.88-3.86 (dd, J = 10.0, 3.0 Hz, 1H), 3.79-3.76 (dd, J = 10.0, 6.0 Hz, 1H), 2.60-2.57 (m, 1H), 2.47-2.42 (m, 1H), 2.01-1.95 (m, 2H), 1.85-1.81 (m, 1H), 1.77-1.70 (m, 1H), 1.06 (s, 9H); **¹³C NMR** (125 MHz, CDCl₃) δ 171.4, 80.6,

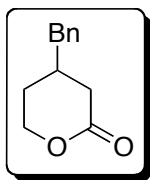
65.6, 30.1, 24.7, 18.5, 18.1, 18.1, 12.1. **HRMS** (CI/NH₃) *m/z* calcd. for C₁₅H₃₀O₃Si [M+NH₄]⁺: 304.2308, found: 304.2306.

5-Phenyl-tetrahydropyran-2-one (**83g**)



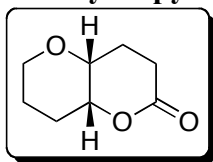
Lactone **83g** was synthesized according to the general procedure as an impure colourless oil (impure, ~50% purity). *R_f* = 0.30 (50% ethyl acetate in hexanes). **¹H NMR** (500 MHz, CDCl₃) δ 7.29-7.15 (m, 5H), 4.48 (dddd, *J* = 11.1, 6.9, 4.4, 2.1 Hz, 1H), 4.31 (dd, *J* = 11.6, 11.6 Hz, 1H), 3.22-3.16 (m, 1H), 2.77 (dd, *J* = 6.3, 4.2 Hz, 1H), 2.68 (dd, *J* = 10.3, 7.6 Hz, 1H), 2.20-2.12 (m, 2H). Spectral data matched those previously reported.¹²⁸

Tetrahydro-4-(phenylmethyl)-2H-pyran-2-one (**83h**)



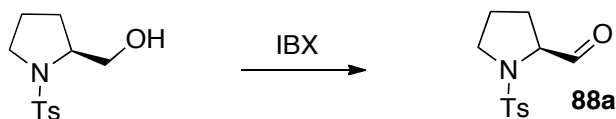
Lactone **83h** was synthesized by following the general procedure. The crude mixture was dissolved in CH₂Cl₂ and then quickly passed through a pad of silica to yield the pure product as a colorless oil (27 mg, 98% yield). **FTIR** *v*_{max} (cm⁻¹): 2917, 1736, 1251, 1219, 1082; **¹H NMR** (500 MHz, CDCl₃) δ 7.33-7.15 (m, 5H), 4.43-4.39 (m, 1H), 4.25-4.22 (m, 1H), 2.67-2.64 (m, 3H), 1.93-1.89 (m, 2H), 1.93-1.89 (m, 1H), 1.65-1.54 (m, 1H), 1.34-1.26 (m, 1H); **¹³C NMR** (125 MHz, CDCl₃) δ 171.1, 138.6, 129.2, 129.1, 126.8, 68.7, 42.5, 36.5, 33.7, 28.7; **HRMS** (EI⁺) *m/z* calcd. for C₁₂H₁₄O₂ [M]⁺: 190.0994, found: 190.0995.

Hexahydropyrano[3,2-b]pyran-2(3*H*)-one (**83j**)



Lactone **83j** was synthesized by following the general procedure, however, 30 mol % catalyst was required. An aqueous workup was avoided, due to concerns of water solubility, therefore, the reaction was quickly filtered through a small pad of silica and concentrated under reduced pressure. The reaction was purified by column chromatography (100% ethyl acetate, $R_f = 0.38$) to yield a colourless oil (18 mg, 62% yield).^{xvii} **FTIR** ν_{\max} (cm^{-1}): 2950, 1724; **^1H NMR** (500 MHz, CDCl_3) δ 4.32 (s, 1H), 4.00-3.96 (m, 1H), 3.65 (s, 1H), 3.52 (dd, $J = 12.2$ 12.2 Hz, 1H), 2.71-2.63 (m, 1H), 2.48-2.42 (m, 1H), 2.13 (d, $J = 14.1$ Hz, 1H), 2.05-1.90 (m, 3H), 1.77-1.71 (m, 1H), 1.40 (d, $J = 13.7$ Hz, 1H); **^{13}C NMR** (125 MHz, CDCl_3) δ 171.3, 75.5, 69.4, 67.7, 28.3, 25.7, 25.2, 19.5; **HRMS** (EI+) m/z calcd. for $\text{C}_8\text{H}_{12}\text{O}_3$ $[\text{M}]^+$: 156.0785, found: 156.0786.

(*S*)-*N*-Tosylpyrrolidine-2-carbaldehyde (**88a**)

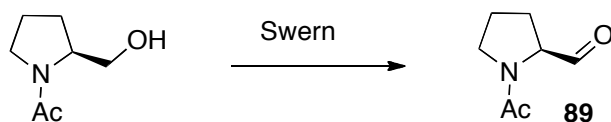


N-Tosyl prolinol¹²⁹ was oxidized using the IBX general procedure, no purification was required (248 mg, 71% yield). **IR** ν_{\max} (cm^{-1}): 3091, 2988, 2867, 1732, 1596, 1339; **^1H NMR** (500 MHz, CDCl_3) δ 9.68 (d, $J = 2.1$ Hz, 1H), 7.72 (d, $J = 8.1$ Hz, 2H), 7.34 (d, $J = 8.0$ Hz, 2H), 3.84-3.81 (ddd, $J = 7.9$, 5.3, 2.2 Hz, 1H), 3.55 (ddd, $J = 10.1$, 6.6, 5.1 Hz, 1H), 3.18 (ddd, $J = 9.0$, 7.3, 7.3 Hz, 1H), 2.44 (s, 3H), 2.07-2.02 (m, 1H), 1.83-1.77 (m, 2H), 1.67-1.62 (m, 1H); **^{13}C NMR** (125 MHz, CDCl_3) δ 200.3, 144.9, 133.7, 130.1,

^{xvii} The yield was determined based on the NMR purity of the starting material.

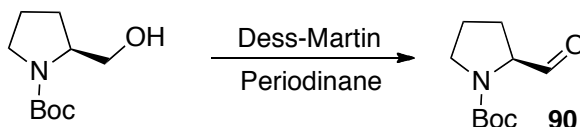
127.9, 66.7, 49.4, 27.8, 24.9, 21.8; **HRMS** (Cl^+/NH_3) m/z calcd. for $\text{C}_{12}\text{H}_{19}\text{N}_2\text{O}_3\text{S}$ $[\text{M}+1]^+$: 271.1116, found: 271.1120.

(S)-N-Acetylpyrrolidine-2-carbaldehyde (89)



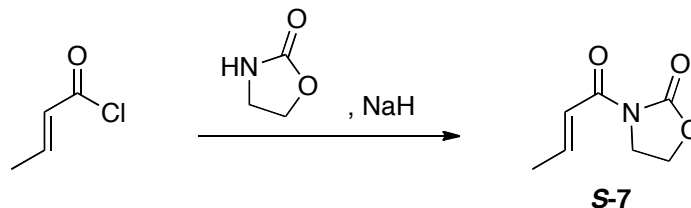
The aldehyde was obtained from a Swern oxidation of *N*-Acetyl L-prolinol¹³⁰ in 47% yield (94 mg, light yellow oil). **¹H NMR** (500 MHz, CDCl_3) δ 9.54 (d, $J = 2.1$ Hz, 1H), 4.45 (ddd, $J = 5.1, 5.1, 5.1$ Hz, 1H), 3.64-3.59 (m, 1H), 3.56-3.51 (m, 1H), 2.13 (s, 3H), 2.08-1.92 (m, 4H). Spectral data matched those previously reported.¹³¹

(2S)-N-(tert-Butoxycarbonyl)pyrrolidine-2-carboxaldehyde (90)



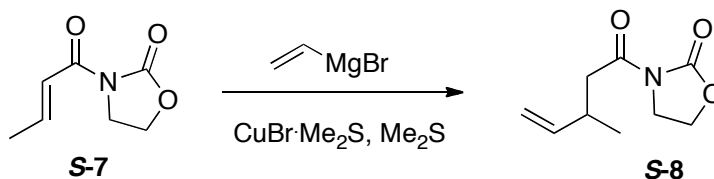
N-Boc L-prolinol¹³² was oxidized with Dess-Martin periodinane using the general procedure as a white solid (35 mg, 80% yield) after purification by column chromatography (50% ethyl acetate in hexanes, $R_f = 0.35$). Mixture of rotamers (3:2): **¹H NMR** (500 MHz, CDCl_3) δ 9.55 (d, $J = 10.5$ Hz, 1H), 9.46 (d, $J = 2.6$ Hz, 1H), 4.06-4.04 (m, 1H), 3.57-3.55 (m, 1H), 3.57-3.43 (m, 4H), 1.99-1.86 (m, 8H), 1.48 (s, 9H), 1.43 (s, 9H). Spectral data matched those previously reported.¹³³

3-(3-methylpent-4-enoyl)oxazolidin-2-one (*S*-7)¹³⁴



NaH (524 mg, 13.1 mmol) was added in two portions to 2-oxazolidin-2-one in dry THF (44 mL, 0.2 M) at 0 °C, under inert atmosphere. The resulting reaction mixture was stirred for 15 min at room temperature. Crotonyl chloride (1.10 mL, 11.4 mmol) was added dropwise, and then stirred for 10 h at room temperature. The reaction was quenched with sat. $\text{NH}_4\text{Cl}_{(\text{aq})}$, extracted with EtOAc (3×20 mL), the combined organic extracts were washed with brine, dried over Na_2SO_4 , then concentrated under reduced pressure. The crude product was purified by column chromatography (50% ethyl acetate in hexanes, $R_f = 0.26$) to afford *S*-7 as a colorless oil (958 mg, 71% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.27-7.24 (m, 1H), 7.21-7.14 (m, 1H), 4.42 (t, $J = 8.0$ Hz, 2H), 4.06 (t, $J = 8.4$ Hz, 2H), 1.96 (d, $J = 6.5$ Hz, 3H). Spectral data matched those previously reported.¹³⁵

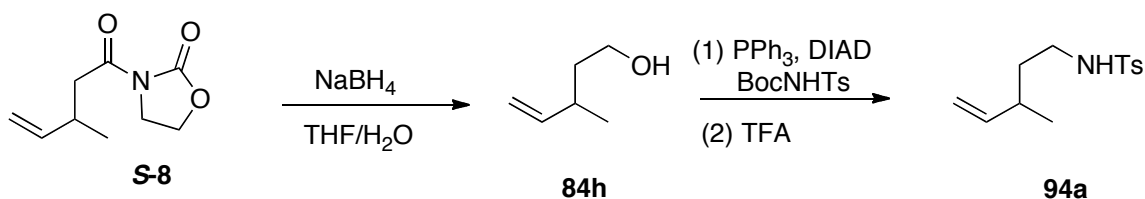
3-(3-Methylpent-4-enoyl)oxazolidin-2-one (*S*-8)¹³⁶



Me_2S (13 mL, 0.66 M) was added to CuBrMe_2S (2.72 g, 13.2 mmol) in dry THF (38 mL) at -78 °C, under inert atmosphere. Vinyl magnesium bromide (26.5 mL, 26.5 mmol) was slowly added at -78 °C and stirred for 15 min. Substrate *S*-7 in dry THF (2 mL) was

added dropwise over 30 min., stirred for 1 h at -78 °C, then warmed up to room temperature over 20 h. The reaction mixture was poured into sat. NH₄Cl (aq) (40 mL), the organic layer was separated, then the resulting aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic extract were washed with 15% NH₄OH (2 × 30 mL), water, brine, dried over Na₂SO₄, then concentrated under reduced pressure. The crude product was purified by column chromatography (50% ethyl acetate in hexanes, R_f = 0.36) to afford **S-8** as a colourless oil (1.080 g, 67% yield). **FTIR** ν_{max} (cm⁻¹): 3534, 3383, 2967, 2927, 1780, 1702, 1642, 1480, 1389, 1290, 1221, 1103, 1040, 919, 761, 621; **¹H NMR** (500 MHz, CDCl₃) δ 5.82-5.75 (m, 1H), 5.01 (d, J = 18.4 Hz, 1H), 4.93 (d, J = 10.1 Hz, 1H), 4.39 (t, J = 7.4, 7.4 Hz, 2H), 4.00 (t, J = 8.6, 8.6 Hz, 2 H), 3.04-2.98 (m, 1H), 2.89-2.84 (m, 1H), 2.79-2.72 (m, 1H), 1.07 (d, J = 6.7 Hz, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 172.3, 153.7, 142.8, 113.6, 62.1, 42.7, 41.7, 34.1, 20.1; **HRMS** (EI⁺) m/z calc for C₉H₁₃NO₃ [M]⁺: 183.0895, found: 183.0891.

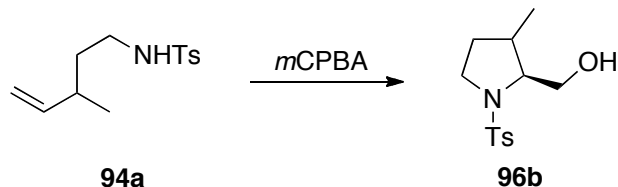
4-Methyl-*N*-(3-methylpent-4-enyl)benzenesulfonamide (**94a**)



NaBH₄ (278 mg, 7.35 mmol) was added to 3-(3-methylpent-4-enoyl)oxazolidin-2-one (521 mg, 2.85 mmol) in THF (14 mL) and distilled water (2 mL) at 0 °C. The reaction was stirred at room temperature for 15 h. The reaction was diluted with distilled water (3 mL), the organic layer was separated, and the resulting aqueous layer was extracted with diethyl ether (3 × 5 mL). The organic extracts were combined and dried over Na₂SO₄,

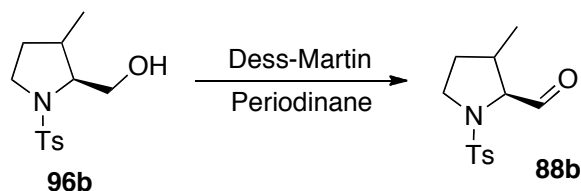
then concentrated under reduced pressure. Alcohol substrate **84h** was used without further purification. **¹H NMR** (500 MHz, CDCl₃) δ 5.76-5.68 (m, 1H), 5.02 (d, *J* = 17.6 Hz, 1H), 4.95 (d, *J* = 10.5 Hz, 1H), 4.67 (t, *J* = 7.4 Hz, 2H), 1.03 (d, *J* = 6.7 Hz, 3H). TsNHBoc (1.00 g, 3.71 mmol) was added to alcohol **84h** and PPh₃ (1.493 g, mmol) in dry THF at room temperature. DIAD (840 μL, 4.28 mmol) was added dropwise, then the flask was covered with aluminum foil. The reaction was stirred for 3 h, then concentrated under reduced pressure. The Boc-intermediate was isolated by column chromatography (10% ethyl acetate in hexanes, *R_f* = 0.22) as a impure colorless oil. The Boc-intermediate was then diluted with CH₂Cl₂ (3 mL, 1 M), then TFA (3 mL) was added at 0 °C and stirred at room temperature for 30 min. The resulting reaction mixture was quenched with sat. NaHCO₃ (aq), diluted with EtOAc, the organic layer was separated, then washed with sat. NaHCO₃ (aq) (5 × 10 mL). The resulting organic extract was dried over Na₂SO₄, then concentrated under reduced pressure. The product was isolated by column chromatography (10% ethyl acetate in hexanes, *R_f* = 0.10) to yield the title sulfonamide **94a** as a light yellow oil (487 mg, 68% yield over 3 steps). **FTIR** ν_{max} (cm⁻¹): 3283, 2963, 2927, 1599, 1421, 1325, 1160, 1120, 998, 815, 663; **¹H NMR** (500 MHz, CDCl₃) δ 7.74 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 7.8 Hz, 2H), 5.58-5.51 (m, 1H), 4.91-4.87 (m, 2H), 2.98-2.85 (m, 2H), 2.41 (s, 3H), 2.17-2.09 (m, 1H), 1.49-1.37 (m, 2H), 0.91 (d, *J* = 6.9 Hz, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 143.4, 143.3, 137.2, 129.8, 127.3, 113.9, 41.5, 36.2, 35.5, 21.6, 20.3; **HRMS** (EI⁺) *m/z* calc for C₁₃H₁₉NO₂S [M]⁺: 253.1137, found: 253.1132.

(3-Methyl-*N*-tosylpyrrolidin-2-yl)methanol (**96b**)



Following the *m*CPBA general procedure **96b** was obtained as a colourless oil (141 mg, separable 2:1 mixture of diastereomers, 60% combined yield) after purifying by column chromatography (50% ethyl acetate in hexanes, R_f = 0.39 and 0.27). Characterization data for major diastereomer: **FTIR** ν_{\max} (cm^{-1}): 3518, 2961, 2931, 2876, 1598, 1454, 1341, 1186, 1110, 1093, 817, 672; **^1H NMR** (500 MHz, CDCl_3) δ 7.74 (d, J = 8.15 Hz, 2 H), 7.34 (d, J = 7.9 Hz, 2H), 3.76 (dd, J = 11.6, 3.4 Hz, 1H), 3.64 (dd, J = 11.6, 5.8 Hz, 1H), 3.40 (t, J = 6.9 Hz, 2H), 3.12-3.09 (m, 1H), 2.44 (s, 3H), 2.11-2.00 (m, 1H), 1.89-1.83 (m, 1H), 1.06-0.98 (m, 1H), 0.67 (d, J = 6.8 Hz, 3H); **^{13}C NMR** (125 MHz, CDCl_3) δ 144.0, 134.2, 130.0, 127.8, 69.3, 65.1, 49.1, 36.5, 32.2, 21.7, 18.2; **HRMS** (EI^+) m/z calc for $\text{C}_{13}\text{H}_{20}\text{NO}_3\text{S}$ $[\text{M}+1]^+$: 270.1164, found: 270.1170.

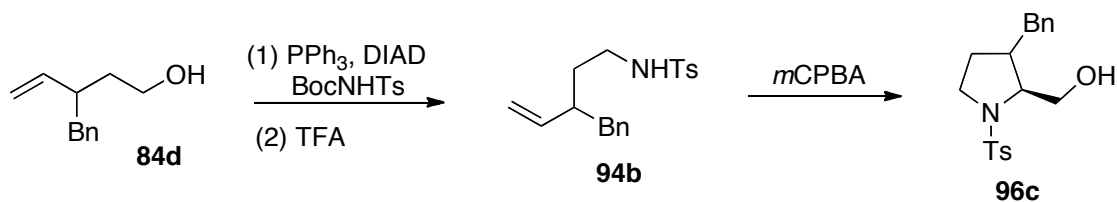
3-Methyl-*N*-tosylpyrrolidine-2-carbaldehyde (**88b**)



Aldehyde **88b** was isolated by column chromatography (25% ethyl acetate in hexanes, R_f = 0.18) as a colorless oil (31 mg, 43% yield, 2:1 mixture of diastereomers). **FTIR** ν_{\max} (cm^{-1}): 2969, 2934, 2877, 1732, 1598, 1383, 1161, 1052, 1018, 817, 667, 593, 550; **^1H NMR** (500 MHz, CDCl_3) δ 9.67 (d, J = 3.7 Hz, 1H, major epimer), 9.59 (d, J = 3.2 Hz,

1H, minor epimer), 7.71-7.68 (m, 4H), 7.35-7.32 (m, 4H), 4.10 (ddd, $J = 7.2, 7.2, 14.5$ Hz, 1H, minor epimer), 3.74-3.69 (m, 3H, both epimer), 3.55-3.50 (m, 1H, minor epimer), 3.35-3.30 (m, 1H, minor epimer), 3.36-3.32 (m, 1H, minor epimer), 3.18 (ddd, $J = 9.0, 9.0, 16.5$ Hz, 1H, major epimer), 2.44 (s, 3H, minor epimer), 2.43 (s, 3H, major epimer), 2.38-2.29 (m, 2H, both epimer), 2.00-1.94 (m, 1H, minor epimer), 1.90-1.84 (m, 1H, major epimer), 1.69-1.61 (m, 1H, major epimer), 1.27-1.23 (m, 1H, major epimer), 1.03 (d, $J = 7.1$ Hz, 3H, major epimer), 1.86 (d, $J = 6.7$ Hz, 3H, minor epimer); ^{13}C NMR (125 MHz, CDCl_3) δ 201.5, 199.5, 144.3, 144.2, 134.0, 133.7, 130.1, 130.0, 128.0, 127.8, 73.4, 69.1, 48.3, 38.3, 36.2, 33.4, 33.0, 21.8, 21.7, 16.8, 14.7, 14.4; HRMS (Cl^+/NH_3) m/z calc for $\text{C}_{13}\text{H}_{18}\text{NO}_3\text{S}$ $[\text{M}+1]^+$: 268.1007, found: 268.1007.

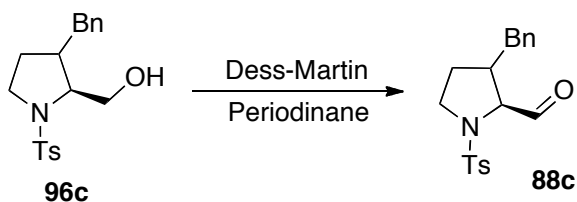
(3-Benzyl-1-tosylpyrrolidin-2-yl)methanol (96c)



94b was synthesized using the general Mitsunobu/deprotection procedure. Crude product was filtered through a pad of silica, washed with 25% ethyl in hexanes, the filtrate was then concentrated. The crude product was then subjected to the epoxidation/cyclization general method B to yield the pure alcohol **96c** as a yellow oil (388 mg, 35% yield over 3 steps, 2.3:1 dr) after purification by column chromatography (25% ethyl acetate in hexanes, $R_f = 0.30$). **Major diastereomer:** ^1H NMR (500 MHz, CDCl_3) δ 7.74 (d, $J = 8.4$ Hz, 2H), 7.35 (d, $J = 8.0$ Hz, 2H), 7.27-7.24 (m, 2H), 7.20-7.17 (m, 1H), 7.06 (d, $J = 7.4$ Hz, 2H), 3.93-3.90 (m, 1H), 3.75-3.68 (m, 1H), 3.61 (dd, $J = 9.3, 9.3$ Hz, 1H), 3.02

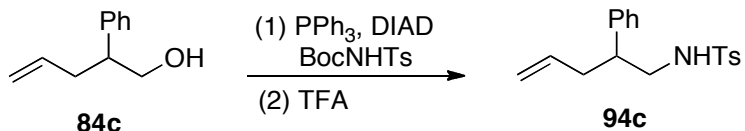
(ddd, $J = 17.2, 9.9, 7.3$ Hz, 1H), 2.80 (dd, $J = 13.9, 5.7$ Hz, 1H), 2.72 (dd, $J = 5.2, 5.2$ Hz, 1H), 2.61 (d, $J = 14.1, 10.3$ Hz), 2.46 (s, 3H), 1.93-1.90 (m, 1H), 1.86-1.77 (m, 1H), 1.71-1.67 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 144.0, 140.0, 133.8, 130.0, 128.6, 128.6, 127.8, 126.4, 63.6, 62.9, 48.4, 43.6, 35.5, 30.1, 21.7.

3-Benzyl-1-tosylpyrrolidine-2-carbaldehyde (**88c**)



Aldehyde **88c** was obtained by the oxidation of **96c** using the outlined Dess-Martin periodinane procedure as a yellow oil (39 mg, 56% yield, 1.7:1 dr). Major diastereomer: ^1H NMR (500 MHz, CDCl_3) δ 9.77 (d, $J = 3.8$ Hz, 1H), 7.70 (d, $J = 8.6$ Hz, 2H), 7.34 (d, $J = 8.0$ Hz, 2H), 7.27-7.25 (m, 2H), 7.21-7.18 (m, 1H), 7.07 (d, $J = 7.4$ Hz, 2H), 3.95-3.93 (m, 1H), 3.75-3.70 (m, 1H), 3.11 (ddd, $J = 16.4, 9.2, 6.9$ Hz, 1H), 2.90 (ddd, $J = 9.9, 9.9, 9.9$ Hz, 1H), 2.48-2.40 (m, 2H), 2.44 (s, 3H), 1.76-1.72 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 201.0, 144.3, 139.2, 134.0, 130.1, 128.8, 128.7, 127.8, 126.8, 68.5, 48.1, 45.6, 35.5, 30.7, 21.7.

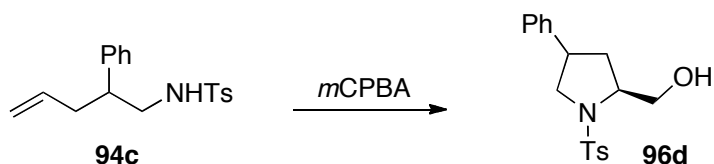
4-Methyl-*N*-(2-phenylpent-4-enyl)benzenesulfonamide (**94c**)



Substrate was synthesized from 2-phenylpent-4-en-1-ol **84c** using the general Mitsunobu procedure. Sulfonamide was purified by column chromatography (20% ethyl acetate in

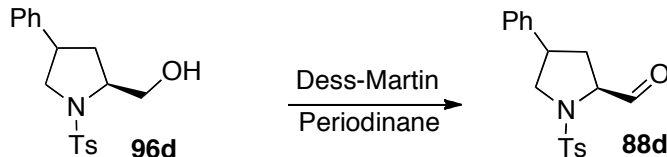
hexanes, $R_f = 0.26$) as a colorless oil (560 mg, 99% yield). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.64 (d, $J = 8.0$ Hz, 2H), 7.29-7.26 (m, 5H), 7.03 (d, $J = 7.8$ Hz, 2H), 5.63-5.55 (m, 1H), 4.97 (d, $J = 10.5$ Hz, 1H), 4.95 (d, $J = 9.5$ Hz, 1H), 4.19-4.16 (m, 1H), 3.34-3.29 (m, 1H), 3.02-2.97 (m, 1H), 2.76 (ddd, $J = 14.3, 6.7, 6.7$ Hz, 1H), 2.43 (s, 3H), 2.37-2.28 (m, 2H). Spectral data matched those previously reported.¹³⁷

(4-Phenyl-*N*-tosylpyrrolidin-2-yl)methanol (96d)



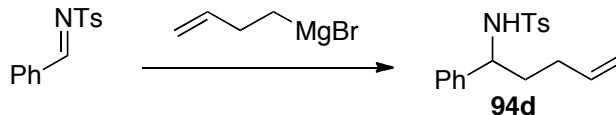
The alcohol substrate was synthesized using the *m*CPBA general protocol, purified by column chromatography (8% ethyl acetate in dichloromethane, $R_f = 0.14$) to furnish the desired substrate in mixture of inseparable diastereomers (2:1 dr) in a combined yield of 81% (156 mg). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.89 (d, $J = 8.2$ Hz, 2H), 7.66 (d, $J = 8.1$ Hz, 2H), 7.38 (d, $J = 8.1$ Hz, 2H), 7.35-7.20 (m, 10 H), 7.09 (d, $J = 7.4$ Hz, 2H), 4.39-4.35 (m, 1H), 3.92-3.85 (m, 2H), 3.81-3.71 (m, 2H), 3.36 (ddd, $J = 11.4, 11.4, 11.4$ Hz, 1H), 3.32 (ddd, $J = 7.9, 7.9, 7.9$ Hz, 1H), 3.11-3.04 (m, 1H), 3.00-2.93 (m, 2H), 2.74-2.70 (m, 1H), 2.65 (dd, $J = 4.6, 4.6$ Hz, 1H), 2.60-2.54 (m, 1H), 2.48 (s, 3H), 2.43 (s, 3H), 2.36-2.34 (m, 1H), 2.29-2.24 (m, 1H), 1.96-1.86 (m, 2H), 1.65-1.59 (m, 1H). Spectral data matched those previously reported.¹³⁸

(4-Phenyl-*N*-tosylpyrrolidin-2-yl)methanol (88d)



Alcohol was oxidized using the DMP general procedure. The resulting aldehyde was purified by column chromatography (33% ethyl acetate in hexanes, $R_f = 0.29$) to afford a colourless oil (95 mg, 70% yield, 1:1 dr). **FTIR** ν_{max} (cm^{-1}): 3063, 3030, 2923, 1734, 1597, 1496, 1454, 1347, 1306, 1185, 1162, 1107, 1091, 1029, 1016, 817, 700, 666, 594, 549; **^1H NMR** (500 MHz, CDCl_3) δ 9.84 (s, 1H), 9.78 (d, $J = 6.0$ Hz, 1H), 7.76-7.74 (m, 4H), 7.39-7.35 (m, 4H), 7.32-7.29 (m, 2H), 7.25-7.20 (m, 4H), 7.14 (d, $J = 7.4$ Hz, 2H), 6.99 (d, $J = 7.0$ Hz, 2H), 4.14-4.09 (m, 1H), 3.96-3.94 (m, 2H), 3.75 (ddd, $J = 10.6, 8.4$ Hz, 1H), 3.57 (ddd, $J = 9.6, 9.6$ Hz, 1H), 3.39-3.28 (m, 1H), 3.09 (ddd, $J = 9.5, 9.5$ Hz, 1H), 2.99 (ddd, $J = 22.1, 13.7$ Hz, 1H), 2.55-2.51 (m, 1H), 2.47 (s, 3H), 2.46 (s, 3H), 2.40-2.34 (m, 1H), 2.14-2.08 (m, 1H), 1.88 (ddd, $J = 11.0, 11.0$ Hz, 1H); **^{13}C NMR** (125 MHz, CDCl_3) δ 200.6, 199.4, 144.6, 144.5, 139.0, 139.0, 133.5, 130.3, 130.2, 129.1, 129.0, 128.0, 127.9, 127.7, 127.5, 127.1, 127.0, 67.2, 66.4, 55.0, 55.0, 43.3, 42.8, 35.5, 34.4, 21.8, 2 C's missing; **HRMS** (Cl^+/NH_3) m/z calc for $\text{C}_{18}\text{H}_{20}\text{NO}_3\text{S}$ $[\text{M}+1]^+$: 330.1164, found: 330.1148.

4-Methyl-*N*-(1-phenylpent-4-enyl)benzenesulfonamide (**94d**)



(*E*)-*N*-Benzylidene-4-methylbenzenesulfonamide¹³⁹ (75 mg, 0.29 mmol) was added slowly to a solution of but-3-enylmagnesium bromide (freshly prepared from 5-bromo-1-butene and magnesium, 0.98 mmol) in diethyl ether (1.96 mL) at 0 °C. After 30 min, the reaction was quenched with aqueous saturated NH₄Cl (5 mL) and extracted with Et₂O (3 × 5 mL). The combined organic layers were dried over Na₂SO₄, and concentrated to afford the title compound (90 mg, 98% yield) as a colourless oil, used without purification. **FTIR** ν_{max} (cm⁻¹): 3064, 2924, 1640, 1456, 1323, 1184; **¹H NMR** (500 MHz, CDCl₃) δ 7.54 (d, *J* = 8.1 Hz, 2H), 7.19-7.12 (m, 3H), 7.09 (d, *J* = 7.9 Hz, 2H), 7.05-6.98 (m, 2H), 5.73-5.64 (m, 1H), 5.33 (d, *J* = 7.2 Hz, 1H), 4.95-4.90 (m, 2H), 4.29 (dd, *J* = 14.6, 7.4 Hz, 1H), 2.34 (s, 3H), 2.00-1.74 (m, 4H); **¹³C NMR** (125 MHz, CDCl₃) δ 143.1, 140.9, 137.9, 137.4, 129.5, 128.6, 127.5, 127.2, 126.7, 115.7, 58.0, 36.8, 30.2, 21.6; **HRMS** (CI⁺/NH₃) *m/z* calc for C₁₈H₂₅N₂O₂S [M+NH₄]⁺: 333.1636, found: 333.1627.

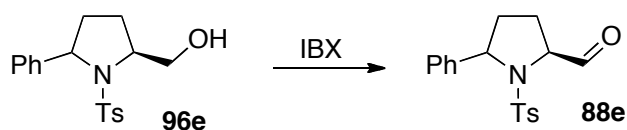
(5-Phenyl-*N*-tosylpyrrolidin-2-yl)methanol (**96e**)



Substrate **96e** was synthesized using the *m*CPBA general procedure. The resulting residue was purified by column chromatography (20% ethyl acetate in hexanes, *R_f* = 0.17) to afford the alcohol (43 mg, 46% yield, 1:1 dr) as a yellow oil. **FTIR** ν_{max} (cm⁻¹):

3275, 3030, 2924, 2864, 1599, 1495, 1456, 1325, 1148; **¹H NMR** (500 MHz, CDCl₃) δ 7.53 (d, *J* = 6.7 Hz, 2H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.16-7.11 (m, 6H), 7.11-7.06 (m, 4H), 7.04-6.97 (m, 4H), 5.53 (br, 2H), 4.35-4.27 (m, 2H), 2.85-2.82 (m, 2H), 2.69 (dd, *J* = 8.9, 4.3 Hz, 2H), 2.38 (dd, *J* = 4.7, 2.6 Hz, 2H), 2.33 (s, 6H), 1.96-1.26 (m, 8H); **¹³C NMR** (125 MHz, CDCl₃) δ 143.2, 143.2, 140.8, 140.7, 140.6, 137.9, 137.8, 129.4, 128.7, 128.7, 127.6, 127.6, 127.6, 127.2, 126.6, 58.3, 58.1, 47.3, 47.2, 34.0, 33.8, 28.9, 28.9, 21.6, 21.6; **HRMS** (CI⁺/NH₃) *m/z* calc for C₁₈H₂₂NO₃S [M+1]⁺: 332.1320, found: 332.1308.

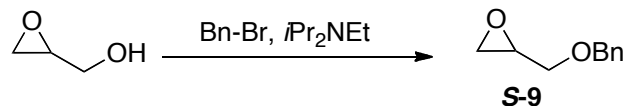
5-Phenyl-*N*-tosylpyrrolidine-2-carbaldehyde (**88e**)



Oxidation by IBX using the general procedure to furnish the aldehyde (21 mg, 39% yield) as a yellow oil after purification by column chromatography (33% ethyl acetate in hexanes, *R_f* = 0.34, 1:1 dr). **FTIR** ν_{max} (cm⁻¹): 3064, 2816, 1733, 1494, 1345, 1216; **¹H NMR** (500 MHz, CDCl₃) δ 9.85 (d, *J* = 1.9 Hz, 1H, major epimer), 9.82 (d, *J* = 3.3 Hz, 1H, minor epimer), 7.67 (d, *J* = 8.2 Hz, 2H, major epimer), 7.36 (d, *J* = 7.5 Hz, 2H, major epimer), 7.16-7.13 (m, 1H, major epimer), 7.07 (t, *J* = 7.7 Hz, 2H, minor epimer), 7.00 (d, *J* = 8.0 Hz, 2H, minor epimer), 6.87 (d, *J* = 7.3 Hz, 2H, minor epimer), 5.22 (dd, *J* = 7.8, 1.9 Hz, 1H, minor epimer), 4.77 (dd, *J* = 7.3, 5.1 Hz, 2H, major epimer), 4.32 (ddd, *J* = 8.5, 2.9, 2.9 Hz, 1H, minor epimer), 4.15 (ddd, *J* = 7.5, 1.7, 1.7 Hz, major epimer), 2.46-2.43 (m, 1H, minor epimer), 2.42 (s, 3H, major epimer), 2.42-2.38 (m, 1H, major epimer), 2.32 (s, 3H, minor epimer), 2.20-1.80 (m, 4H, both epimers); **¹³C NMR** (125 MHz, CDCl₃) δ 200.2, 199.8, 144.4, 143.3., 141.5, 140.6, 137.4, 134.3, 130.0, 129.3,

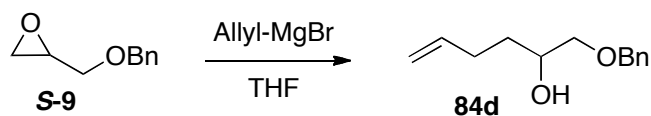
128.7, 128.4, 127.9, 127.7, 127.5, 127.3, 126.9, 126.5, 68.4, 64.6, 35.1, 34.2, 27.2, 25.9, 21.7, 21.6; **HRMS** (Cl^+/NH_3) m/z calc for $\text{C}_{18}\text{H}_{23}\text{N}_2\text{O}_3\text{S}$ $[\text{M}+\text{NH}_4]^+$: 347.1429, found: 347.1438.

2-(Benzyloxymethyl)oxirane (**S-9**)



NaH (1.30 g, 32.2 mmol) was added to a solution of (±)-glycidol (1.50 mL, 26.8 mmol) in anhydrous DMF (89 mL, 0.3 M) at 0 °C, under inert atmosphere. After 5 min, benzyl bromide (4.8 mL, 40.1 mmol) was added; the reaction was then warmed up to rt over 10 h. The reaction was quenched with distilled water (10 mL), then extracted with CH_2Cl_2 (3×25 mL), the combined organic extract was dried over Na_2SO_4 , then concentrated. The crude product was purified by column chromatography (10% ethyl acetate in hexanes, $R_f = 0.20$) to yield the product as a colourless oil (1.98 mg, 45% yield). **^1H NMR** (500 MHz, CDCl_3) δ 7.45-7.19 (m, 5H), 4.59 (dd, $J = 27.7, 11.9$ Hz, 2H), 3.77 (dd, $J = 11.4, 2.8$ Hz, 1H), 3.45 (d, $J = 11.4, 5.7$ Hz, 1H), 3.20-3.18 (m, 1H), 2.80 (dd, $J = 4.8, 4.8$ Hz, 1H), 2.62 (dd, $J = 2.6, 1.8$ Hz, 1H). Spectral data matched those previously reported.¹⁴⁰

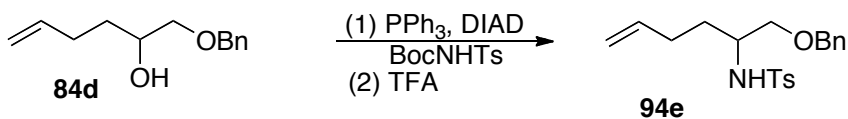
1-(Benzyloxy)hex-5-en-2-ol (**84d**)



Alcohol **84d** was synthesized using the same Grignard addition procedure for the

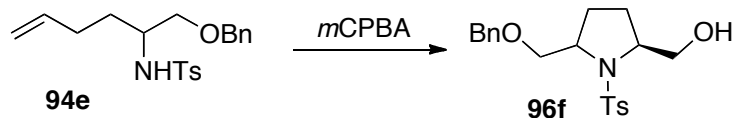
synthesis of alcohol **84a** to yield the product as a colourless oil (413 mg, 34% yield). **¹H NMR** (500 MHz, CDCl₃) δ 7.38-7.29 (m, 5H), 5.86-5.80 (m, 1H), 5.04 (d, *J* = 17.0 Hz, 1H), 4.98 (d, *J* = 10.1 Hz, 1H), 4.56 (s, 2H), 3.86-3.81 (m, 1H), 3.51 (dd, *J* = 9.4, 3.9 Hz, 1H), 3.35 (dd, *J* = 7.9, 7.9 Hz, 1H), 2.49 (br s, 1H), 2.25-2.20 (m, 1H), 2.17-2.11 (m, 1H), 1.62-1.50 (m, 2H) Spectral data matched those previously reported by Li Wang.⁹⁸

***N*-(1-Benzyloxy)hex-5-en-2-yl)-4-methylbenzenesulfonamide (94e)**



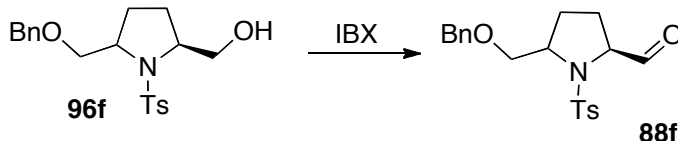
The corresponding sulfonamide was synthesized from 1-(benzyloxy)hex-5-en-2-ol **84d** using the stated Mitsunobu protocol. Purified by chromatography (30% ethyl acetate in hexanes, *R_f* = 0.27) to afford the sulfonamide **93e** as colorless oil in 72% yield over 2 steps (413 mg). **FTIR** ν_{max} (cm⁻¹): 3064, 2924, 2826, 1640, 1453, 1208, 1161; **¹H NMR** (500 MHz, CDCl₃) δ 7.71 (d, *J* = 8.1 Hz, 2H), 7.35-7.20 (m, 7H), 5.71-5.66 (m, 1H), 4.92 (ddd, *J* = 4.2, 1.5, 1.5 Hz, 2H), 4.90-4.80 (m, 1H), 4.34 (s, 2H), 3.37-3.33 (m, 1H), 3.31 (dd, *J* = 9.4, 3.5 Hz, 1H), 3.20 (dd, *J* = 9.3, 4.1 Hz, 1H), 2.42 (s, 3H), 2.04-1.94 (m, 2H), 1.60 (q, *J* = 14.7, 7.3 Hz, 2H); **¹³C NMR** (125 MHz, CDCl₃) δ 143.3, 138.4, 137.9, 137.8, 129.8, 128.6, 128.0, 127.8, 127.3, 115.4, 73.4, 71.2, 53.3, 32.0, 29.9, 21.7; **HRMS** (CI⁺/NH₃) *m/z* calc for C₂₀H₂₉N₂O₃S [M+NH₄]⁺: 377.1898, found: 377.1909.

(5-(Benzyloxymethyl)-*N*-tosylpyrrolidin-2-yl)methanol (96f)



Synthesized using the *m*CPBA general procedure. Purified by column chromatography (30% ethyl acetate in hexanes, $R_f = 0.30$) to furnish the desired alcohol as a mixture of diastereomers (2:1) in 27% yield as a yellow oil (459 mg). Characterization data for major diastereomer: **FTIR** ν_{\max} (cm^{-1}): 3031, 2923, 1598, 1495, 1327, 1206, 1092, 918, 739, 550; **^1H NMR** (500 MHz, CDCl_3) δ 7.70 (d, $J = 8.1$ Hz, 2H), 7.34-7.27 (m, 3H), 7.23 (d, $J = 8.1$ Hz, 2H), 7.19 (d, $J = 6.8$ Hz, 2H), 5.02 (d, $J = 8.4$ Hz, 1H), 4.31 (dd, $J = 12.7$, 12.7 Hz, 2H), 3.42-3.36 (m, 1H), 3.29 (dd, $J = 9.4$, 3.6 Hz, 1H), 3.16 (dd, $J = 9.4$, 4.4 Hz, 1H), 2.85 (ddd, $J = 6.6$, 3.7, 3.7 Hz, 1H), 2.70 (dd, $J = 4.5$ Hz, 1H), 2.41 (br s, 1H), 2.39 (s, 3H), 1.71-1.57 (m, 3H), 1.43-1.37 (m, 1H); **^{13}C NMR** (125 MHz, CDCl_3) δ 143.4, 138.2, 137.8, 129.7, 128.6, 127.9, 127.8, 127.1, 73.3, 71.2, 53.2, 51.9, 47.3, 29.0, 28.5, 21.7; **HRMS** (CI^+/NH_3) m/z calc for $\text{C}_{20}\text{H}_{26}\text{NO}_4\text{S}$ $[\text{M}+1]^+$: 376.1582, found: 376.1595.

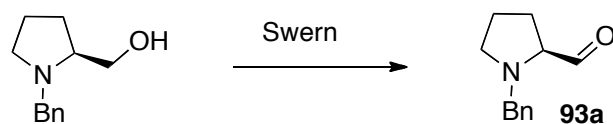
5-(Benzyloxymethyl)-*N*-tosylpyrrolidine-2-carbaldehyde (88f)



IBX oxidation was performed with the general procedure to afford the aldehyde in 36% yield as a yellow oil (2:1 mixture of diastereomers). Characterization data for major diastereomer: **FTIR** ν_{\max} (cm^{-1}): 3030, 2867, 2702, 1734, 1597, 1495, 1347, 1249, 1205, 1161, 1092, 911, 816, 739, 699; **^1H NMR** (500 MHz, CDCl_3) δ 9.60 (d, $J = 2.6$ Hz, 1H),

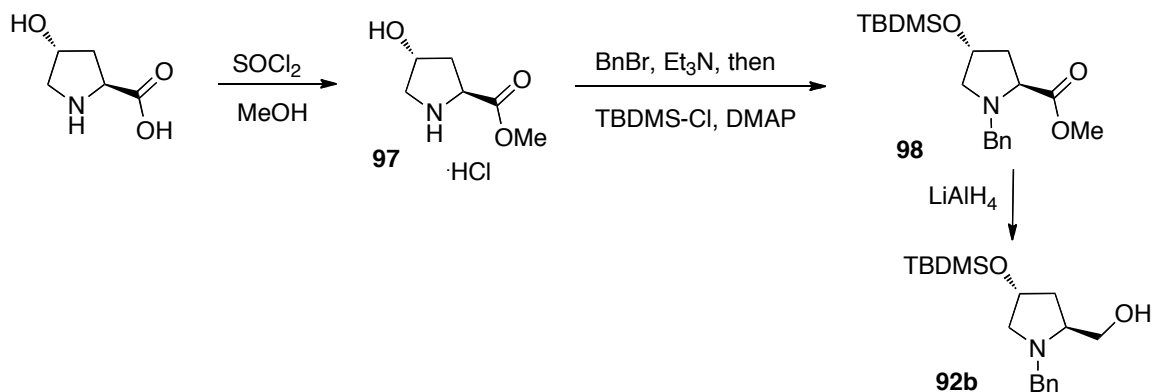
7.72 (d, $J = 8.1$ Hz, 2H), 7.38-7.21 (m, 7H), 4.57 (dd, $J = 16.8, 11.9$ Hz, 2H), 3.89-3.83 (m, 1H), 3.82 ddd, $J = 15.7, 7.8, 2.4$ Hz, 1H), 3.75 (dd, $J = 9.4, 3.2$ Hz, 1H), 3.62 (dd, $J = 9.3, 6.9$ Hz, 1H), 2.45 (s, 3H), 2.09-1.56 (m, 4H); ^{13}C NMR (125 MHz, CDCl_3) δ 200.3, 144.4, 138.1, 130.1, 128.6, 128.4, 127.9, 127.8, 127.8, 73.7, 73.1, 68.1, 60.8, 28.4, 26.3, 21.7; HRMS (Cl^+/NH_3) m/z calc for $\text{C}_{20}\text{H}_{27}\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{NH}_4]^+$: 391.1691, found: 391.1690.

(*S*)-*N*-Benzylpyrrolidine-2-carbaldehyde (93a**)**



Substrate **93a** was obtained as a brown oil (140 mg, 69% yield) using the Swern oxidation procedure from *N*-Bn L-prolinol.¹⁴¹ ^1H NMR (500 MHz, CDCl_3) δ 9.31 (d, $J = 4.0$ Hz, 1H), 7.32 -7.31(m, 5H), 3.75 (d, $J = 13.4$ Hz, 1H), 3.66 (d, $J = 13.4$ Hz, 1H), 3.13-3.10 (m, 1H), 3.01-2.97 (m, 1H), 2.40 (ddd, $J = 17.2, 8.8, 8.8$ Hz, 1H), 2.05-2.97 (m, 1H), 1.92-1.81 (m, 3H). Spectral data matched those previously reported.¹⁴²

((2*S*,4*R*)-*N*-Benzyl-4-(*tert*-butyldimethylsilyloxy)pyrrolidin-2-yl)methanol (92b**)**

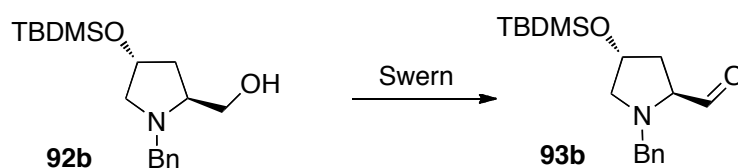


92b was synthesized according to literature procedure.¹⁴³ Thionyl chloride (370 μ L, 5.04 mmol) was added dropwise to *trans*-4-hydroxy-L-proline in methanol (17 mL, 0.3M) at 0 °C. After 5 min, the reaction was refluxed at 65 °C for 1 h. The reaction was warmed up to room temperature, then concentrated to yield **97** as a white solid. ¹H NMR (500 MHz, D₂O) δ 4.75-4.73 (m, 2H), 3.89 (s, 3H), 3.57 (d, *J* = 12.5 Hz, 1H), 3.45 (d, *J* = 12.5 Hz, 1H), 2.55-2.51 (m, 1H), 2.36-2.25 (m, 1H), 2.25 (s, 2H).

To **97** substrate was added dry CH₂Cl₂ (4.4 mL, 0.95 M), then Et₃N (2.35 mL, 16.8 mmol) was added at room temperature under inert atmosphere. BnBr (862 μ L, 5.04 mmol) was added and stirred at room temperature for 10 min, and then the reaction was refluxed for 5 h. The reaction was cooled to rt, TBDMS-Cl (760 mg, 5.04 mmol) was added, followed by DMAP (51 mg, 0.42 mmol). Stirred at rt for an additional 12 h. The reaction was quenched with sat. Na₂CO₃ (aq) until the pH of the solution is ~ 10. CH₂Cl₂ was added, the organic layer was separated, and the resulting aqueous layer was extracted with EtOAc (10 mL). The combined organic extract was dried over Na₂SO₄, and then concentrated under reduced pressure to furnish the desired **98** substrate, used without purification.

LiAlH₄ (319 mg, 8.40 mmol) in dry THF (8 mL) was cooled to 0 °C. Ester **98** (4.20 mmol) in THF (3 mL) was added dropwise. The reaction was stirred at 0°C for 10 min, then refluxed for 2 h. The reaction was cooled to 0°C, then quenched with distilled water (1 mL), followed by the addition of 4 M NaOH (500 mL), distilled water (1 mL) and MgSO₄. The resulting suspension was stirred for 30 min, then filtered through Celite®, the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (50% ethyl acetate in hexanes, *R_f* = 0.28) to afford the desired alcohol **92b** as a colourless oil (1.065 g, 83% yield over 4 steps). ¹H NMR (500 MHz, CDCl₃) δ 7.31-7.25 (m, 4H), 7.16-7.05 (m, 1H), 4.42-4.38 (m, 1H), 3.95 (d, *J* = 13.2 Hz, 1H), 3.64 (dd, *J* = 11.0, 3.7 Hz, 1H), 3.45 (d, *J* = 13.0 Hz, 1H), 3.37 (d, *J* = 12.3 Hz, 1H), 3.12 (dd, *J* = 10.1, 5.9 Hz, 1H), 3.08-3.04 (m, 1H), 2.66 (br s, 1H), 2.35 (dd, *J* = 9.7, 5.9 Hz, 1H), 2.07 (ddd, *J* = 13.9, 7.3, 7.3 Hz, 1H), 1.82 (ddd, *J* = 13.0, 8.6, 4.6 Hz, 1H), 0.87 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H). Spectral data matched those previously reported.¹⁴³

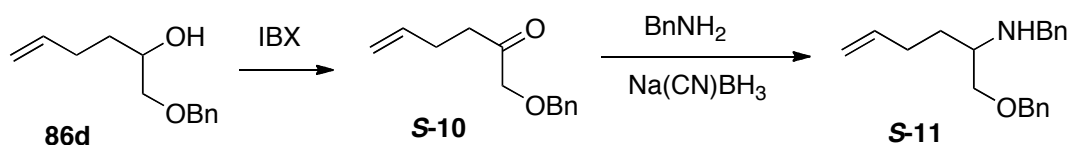
((2*S*,4*R*)-*N*-Benzyl-4-(*tert*-butyldimethylsilyloxy)pyrrolidin-2-yl)methanol (93b**)**



Aldehyde **93b** was synthesized using the Swern oxidation conditions to furnish the desired product (95 mg, 96% yield). FTIR ν_{max} (cm⁻¹): 3064, 3029, 2955, 2929, 2857, 1731, 1496, 1472, 1463, 1454, 1361, 1256, 1116, 1006, 837, 776, 700; ¹H NMR (500 MHz, CDCl₃) δ 9.29 (d, *J* = 4.0 Hz, 1H), 7.33-7.32 (m, 4H), 7.29-7.26 (m, 1H), 4.38 (ddd, *J* = 10.4, 5.2, 5.2 Hz, 1H), 3.80 (d, *J* = 12.9 Hz, 1H), 7.45 (d, *J* = 12.9 Hz, 1H),

3.35 (ddd, $J = 8.4, 8.4, 4.0$ Hz, 1H), 3.31 (dd, $J = 10.0, 5.4$ Hz, 1H), 2.44 (dd, $J = 10.0, 4.7$ Hz, 1H), 2.07-2.01 (m, 1H), 1.94-1.92 (m, 1H), 0.89 (s, 9H), 0.05 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 202.6, 138.5, 129.3, 128.6, 127.7, 71.1, 70.8, 62.7, 60.3, 36.9, 26.0, 18.2, -4.6, -4.7; HRMS (CI^+/NH_3) m/z calc for $\text{C}_{18}\text{H}_{30}\text{NO}_2\text{Si}$ $[\text{M}+1]^+$: 320.2046, found: 320.2036.

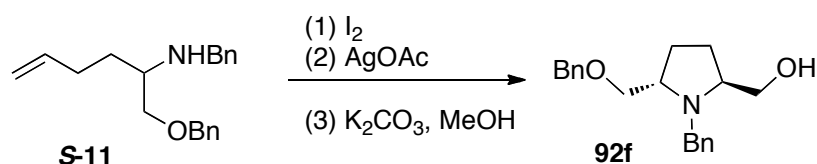
***N*-Benzyl-1-(benzyloxy)hex-5-en-2-amine (*S*-11)¹⁴⁴**



1-(Benzyloxy)hex-5-en-2-ol **86d** (144 mg, 0.699 mmol) was oxidized using the IBX general procedure, without further purification the crude reaction mixture was dissolved in CH_3CN (3.5 mL, 0.2 M) at rt, opened to air. BnNH_2 (92 μL , 0.839 mmol) was added and stirred for 15 min., followed by the addition of $\text{Na}(\text{CN})\text{BH}_3$ (97 mg, 1.54 mmol). The reaction was stirred for an additional 24 h. The resulting reaction mixture was neutralized to pH 12 with 1 M NaOH, then extracted with CH_2Cl_2 (3×10 mL), the combined organic extract was dried over Na_2SO_4 then concentrated under reduced pressure. Amine **S-11** was purified by column chromatography (33% ethyl acetate in hexanes, $R_f = 0.23$) as a colorless oil (78 mg, 38% yield). FTIR ν_{max} (cm^{-1}): 3327, 3063, 3028, 3002, 2924, 2856, 1640, 1495, 1453, 1363, 1099, 1076, 1028, 996, 910, 734, 697; ^1H NMR (500 MHz, CDCl_3) δ 7.39-7.16 (m, 10H), 5.90-5.79 (m, 1H), 5.02 (d, $J = 14.5$ Hz, 1H), 4.76 (d, $J = 10.2$ Hz, 1H), 4.54 (s, 2H), 3.85-3.76 (m, 2H), 3.56 (dd, $J = 9.4, 4.2$ Hz, 1H), 3.46 (dd, $J = 9.1, 6.0$ Hz, 1H), 2.87-2.84 (m, 1H), 2.15-2.09 (m, 2H), 1.92-1.86 (br s, 1H), 1.70-1.55 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 141.0, 138.8, 138.6, 128.5,

128.5, 128.3, 127.8, 127.7, 127.0, 114.7, 73.3, 72.3, 56.4, 51.4, 31.1, 30.3; **HRMS** (EI⁺) *m/z* calc for C₂₀H₂₅NO [M]⁺: 295.1936, found: 295.1929.

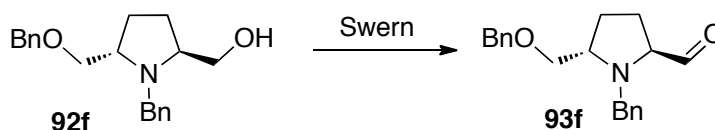
***trans*- (N-Benzyl-5-(benzyloxymethyl)pyrrolidin-2-yl)methanol (92f)**



I₂ (120 mg, 0.473 mmol) was added to amine **S-11** (93 mg, 0.315 mmol) dissolved in CH₂Cl₂ (4 mL) and Et₂O (4 mL) opened to the atmosphere. The reaction was stirred for 15 h at rt, then quenched with sat. Na₂S₂O₃ (aq), and stirred until the disappearance of the reddish color, then the organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extract was dried over Na₂SO₄ then concentrated. Toluene was added (10 mL, 0.031 M) was added, followed by AgOAc (263 mg, 1.58 mmol) and stirred for 2 h. Distilled water was added, followed by sat. NH₄Cl_(aq), extracted with EtOAc (3 × 10 mL), the combined organic extract was dried over Na₂SO₄ then concentrated. MeOH (5 mL, 0.058 M) was added followed by K₂CO₃ (57 mg, 0.41 mmol). The reaction was stirred for 1 h at rt. The reaction was then quenched with sat. NH₄Cl (aq), extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extract was dried over Na₂SO₄ then concentrated. The resulting crude product was purified by column chromatography (20% hexanes in ethyl acetate, R_f = 0.18) to furnish the desired product as a light yellow oil as a inseparable 6:1 mixture of diastereomers (*trans*:*cis*, 36 mg, 37% yield). **FTIR** ν_{max} (cm⁻¹): 3432, 2871, 1495, 1453, 1362, 1208, 1098, 1028, 735, 698; **¹H NMR** (500 MHz, CDCl₃) δ 7.44-7.13 (m, 10H), 4.49 (s, 2H), 3.86 (d, *J* = 13.5 Hz, 1H), 3.79 (d, *J* = 14.0 Hz, 1H), 3.60-3.53 (m, 1H),

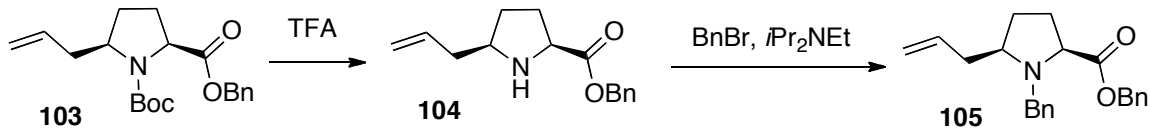
3.45-3.37 (m, 1H), 3.31-3.24 (m, 1H), 3.17-3.12 (m, 1H), 2.62 (br s, 1H), 2.13 (ddd, $J = 18.6, 9.2, 9.2$ Hz, 1H), 1.95- 1.88 (m, 1H), 1.85-1.76 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 140.0, 138.7, 129.1, 128.5, 128.4, 127.7, 127.7, 127.0, 73.5, 73.4, 70.3, 63.1, 62.2, 59.9, 51.8, 28.4, 28.1, 27.5, 27.4; **HRMS** (EI^+) m/z calc for $\text{C}_{20}\text{H}_{25}\text{NO}_2$ $[\text{M}]^+$: 311.1885, found: 311.1888.

***trans*-N-Benzyl-5-(benzyloxymethyl)pyrrolidine-2-carbaldehyde (93f)**



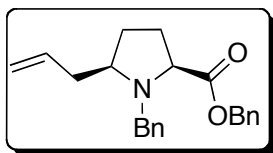
Aldehyde **93f** was obtained as a brown oil using Swern conditions (48 mg, 83% yield, 6:1 *trans/cis*). The identity of each diastereomer was established by comparison of their NMR spectrum with that of aldehyde **91f**. Characterization data for the major (*trans*) diastereomer: **FTIR** ν_{max} (cm^{-1}): 3028, 2941, 2856, 1726, 1495, 1453, 1364, 1210, 1099, 1076, 737, 698; ^1H NMR (500 MHz, CDCl_3) δ 9.34 (d, $J = 3.6$ Hz, 1H), 7.43-7.24 (m, 10H), 4.51 (s, 2H), 3.99 (d, $J = 13.6$ Hz, 1H), 3.88 (d, $J = 13.6$ Hz, 1H), 3.53-3.341 (m, 4H), 2.21-2.13 (m, 1H), 2.10-2.00 (m, 1H), 1.89-1.75 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 203.9, 139.6, 138.6, 129.8, 128.9, 128.6, 128.5, 128.5, 127.8, 127.8, 127.3, 73.5, 71.6, 70.4, 64.5, 60.9, 53.5, 28.7, 28.1, 25.6; **HRMS** (EI^+) m/z calc for $\text{C}_{20}\text{H}_{24}\text{NO}_2$ $[\text{M}]^+$: 310.1807, found: 310.1839.

***cis*-(–)-(2*S*)-Benzyl 5-allyl-1-benzylpyrrolidine-2-carboxylate (**105**)**



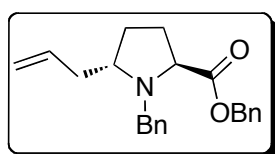
TFA (1.3 mL) was added to a solution of (2*S*)-2-Benzyl 1-*tert*-butyl-5-allylpyrrolidine-1,2-dicarboxylate **103** (4:1 *cis/trans*)^{145,146} (259 mg, 0.751 mmol) in CH₂Cl₂ (2.5 mL, 0.3 M) at rt. The reaction was stirred for 15 h, then slowly quenched with sat. NaHCO₃ (aq), extracted with CH₂Cl₂ (3 × 15 mL), combined organic extract was dried over Na₂SO₄, then concentrated under reduced pressure to furnish the product **104** as a brown oil (168 mg, 91% yield). The product was used without purification.

BnBr (51 μL, 0.432 mmol) was added to a solution of the ester **104** (96 mg, 0.393 mmol) and *i*Pr₂NEt (205 μL, 1.18 mmol) in dry toluene (400 μL) at 0 °C under nitrogen. The reaction was warmed up to rt, then refluxed at 110 °C for 15 h. The reaction was cooled to rt, then quenched with sat. NaHCO₃ (aq), extracted with EtOAc (3 × 5 mL). The combined organic extract was dried over Na₂SO₄, then concentrated under reduced pressure. The product **105** was isolated after column chromatography (25% hexanes in dichloromethane, *R_f* = 0.47 (*trans*-**105**) and *R_f* = 0.31 (*cis*-**105**)) to furnish the *trans*-product (32 mg, 24% yield) as a colourless oil and the *cis*-product as a yellow oil (94 mg, 71% yield).



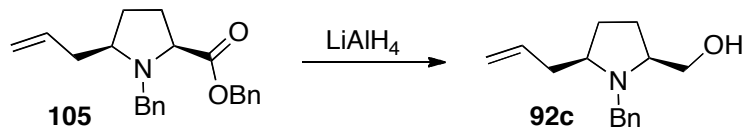
***cis*-105**: [α]_D²³ = –119 (*c* 3.2, CHCl₃); **FTIR** ν_{max} (cm^{–1}): 3065, 2974, 2949, 2877, 2847, 1731, 1495, 1454, 1152, 1029, 995, 748, 698; **¹H NMR** (500 MHz, CDCl₃) δ 7.41–7.34 (m, 5H), 7.29–7.24 (m, 5H), 5.92–5.84 (m, 1H), 5.16 (dd, *J* = 12.3, 12.3 Hz, 1H), 5.10–5.07 (m, 2H), 4.03 (d,

$J = 13.6$ Hz, 1H), 3.73 (d, $J = 13.5$ Hz, 1H), 3.66 (d, $J = 7.5$ Hz, 1H), 3.42-3.38 (m, 1H), 2.41-2.38 (m, 1H), 2.18-2.04 (m, 3H), 1.85-1.79 (m, 1H), 1.71-1.67 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 174.4, 139.9, 136.3, 136.0, 128.8, 128.7, 128.5, 128.4, 128.4, 127.0, 116.7, 65.9, 63.2, 61.1, 52.7, 38.7, 28.7, 27.9; **HRMS** (EI^+) m/z calc for $\text{C}_{22}\text{H}_{25}\text{NO}_2$ $[\text{M}]^+$: 336.1964, found: 336.1967.



trans-105: $[\alpha]_{\text{D}}^{23} = +2.3$ (c 3.2, CHCl_3); **FTIR** ν_{max} (cm^{-1}): 3064, 3030, 2973, 2875, 2807, 1746, 1495, 1454, 1376, 1356, 1271, 1162, 1076, 1029, 994. 913, 750, 698; ^1H NMR (500 MHz, CDCl_3) δ 7.38-7.23 (m, 10H), 5.90-5.82 (m, 1H), 5.07 (d, $J = 18.1$ Hz, 1H), 5.03 (d, $J = 10.4$ Hz, 1H), 4.95 (ddd, $J = 19.4, 12.4, 12.4$ Hz, 2H), 3.98 (d, $J = 13.9$ Hz, 1H), 3.76 (d, $J = 13.9$ Hz, 1H), 3.41 (ddd, $J = 8.1, 6.4$ Hz, 1H), 2.86-2.81 (m, 1H), 2.43-2.39 (m, 1H), 2.20-2.14 (m, 1H), 2.02-1.87 (m, 3H), 1.74-1.66 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 174.6, 138.7, 136.3, 136.1, 129.5, 128.6, 128.2, 128.2, 127.1, 116.5, 66.5, 66.2, 64.3, 57.7, 39.4, 30.0, 28.4; **HRMS** (EI^+) m/z calc for $\text{C}_{22}\text{H}_{25}\text{NO}_2$ $[\text{M}]^+$: 336.1964, found: 336.1973.

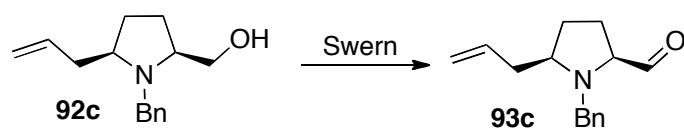
cis-((2S)-5-Allyl-1-benzylpyrrolidin-2-yl)methanol (92c)



LiAlH_4 (10 mg, 0.251 mmol) was added to ester **105** (77 mg, 0.228 mmol, 5:1 dr) in methyl *tert*-butyl ether (650 μL , 0.35 M) at 0 °C under nitrogen. The reaction was stirred for 10 min at rt. Consumption of the starting material was observed by TLC, the reaction was then quenched with distilled water (0.5 mL), followed by the addition of 1 M NaOH

(0.5 mL), diluted with THF (5 mL), and 50 mg Mg_2SO_4 , stirred for 15 min. The suspension was filtered, washed several times with THF, the resulting filtrate was collected and concentrated under reduced pressure. The alcohol **92c** was purified by column chromatography (25% ethyl acetate in hexanes, $R_f = 0.24$) as a colourless oil (33 mg, 62% yield, 5:1 dr). Characterization data for major diastereomer: **FTIR** ν_{max} (cm^{-1}): 3423, 3063, 3028, 2929, 2875, 1640, 1495, 1453, 1210, 1123, 1075, 1029, 993, 912; **^1H NMR** (500 MHz, CDCl_3) δ 7.33-7.24 (m 5H), 5.80-5.72 (m, 1H), 5.03-5.00 (m, 2H), 3.85 (d, $J = 13.6$ Hz, 1H), 3.68 (d, $J = 13.6$ Hz, 1H), 3.27 (dd, $J = 10.6, 3.6$ Hz, 1H), 3.23 (dd, $J = 10.4, 2.1$ Hz, 1H), 2.96-2.92 (m, 1H), 2.91-2.86 (m, 1H), 2.66-2.56 (m, 1H), 2.29-2.24 (m, 1H), 2.07-2.01 (m, 1H), 1.87-1.71 (m, 3H), 1.56-1.51 (m, 1H); **^{13}C NMR** (125 MHz, CDCl_3) δ 139.6, 135.7, 129.2, 128.6, 127.4, 116.9, 65.8, 64.9, 62.8, 57.9, 39.9, 29.9, 27.2; **HRMS** (CI^+/NH_3) m/z calc for $\text{C}_{22}\text{H}_{25}\text{NO}_2$ $[\text{M}+1]^+$: 232.1701, found: 232.1694.

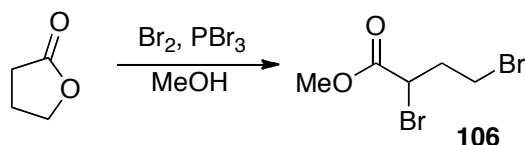
***cis*-(2*S*)-5-Allyl-1-benzylpyrrolidine-2-carbaldehyde (**93c**)**



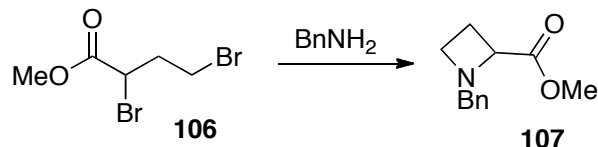
Following the Swern oxidation procedure the aldehyde substrate was obtained as a yellow oil (50 mg, 86% yield, 5:1 *cis:trans*). Characterization data for major diastereomer: **FTIR** ν_{max} (cm^{-1}): 3064, 3029, 2973, 2929, 2807, 1727, 1640, 1495, 1454, 1363, 1335, 1208, 1126, 1075, 1029, 995, 914, 750, 700; **^1H NMR** (500 MHz, CDCl_3) δ 8.99 (d, $J = 4.0$ Hz, 1H), 7.32-7.29 (m, 5H), 5.91-5.82 (m, 1H), 5.10 (d, $J = 20.0$ Hz, 1H), 5.06 (d, $J = 12.3$ Hz, 1H), 4.06 (d, $J = 12.8$ Hz, 1H), 3.47 (d, $J = 13.4$ Hz, 1H), 3.11-3.09

(m, 1H), 2.91-2.86 (m, 1H), 2.45-2.40 (m, 1H), 2.22-2.16 (m, 1H), 1.97-1.90 (m, 1H), 1.88-1.75 (m, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 203.2, 138.7, 135.6, 129.8, 129.0, 128.6, 127.8, 117.0, 73.1, 64.8, 61.2, 58.5, 52.9, 41.2, 30.2, 25.6, 24.8; HRMS (EI^+) m/z calc for $\text{C}_{15}\text{H}_{20}\text{NO}$ $[\text{M}+1]^+$: 230.1545, found: 230.1546.

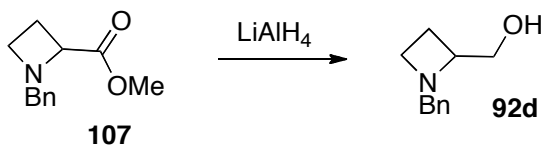
Methyl 2,4-dibromobutanoate (**106**)



PBr_3 (70 μL , 0.724 mmol) was added to γ -butyrolactone (3.0 mL, 39.3 mmol) in a three-neck flask equipped with a condenser and heated to 100 $^\circ\text{C}$, under N_2 . To the stirring solution, Br_2 (2.20 mL, 43.2 mmol) was added dropwise. The reaction was allowed to cool down to rt, then cooled to 0 $^\circ\text{C}$. MeOH (16 mL) was added, followed by conc. HCl was added until the pH <1. The reaction was allowed to stand overnight at rt. Sat. NaHSO_3 (aq) was added until the disappearance of the red color was observed; the aqueous layer was extracted with Et_2O (3×20 mL), the combined organic extract were dried over Na_2SO_4 , then concentrated under reduced pressure. The product **106** was purified by bulb-to-bulb distillation (100 $^\circ\text{C}$ at 20 Torr) as a brown oil (8.163 g, 80% yield). ^1H NMR (500 MHz, CDCl_3) δ 4.53 (dd, $J = 5.9, 5.9$ Hz, 1H), 3.81 (s, 3H), 3.54 (dd, $J = 5.8, 5.8$ Hz, 2H), 2.57-2.48 (m, 2H). Spectral data matched those previously reported.¹⁴⁷

Methyl *N*-benzylazetidine-2-carboxylate (105**)¹⁴⁸**

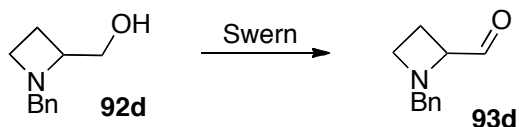
BnNH_2 (1.20 mL, 10.6 mmol) was added to dibromo substrate **106** (500 μL , 3.54 mmol) in CH_3CN (18 mL, 0.2 M) under N_2 at rt. The reaction was heated to reflux and stirred overnight (15 h). The reaction was cooled to rt, then the solid was filtered off and the filtrate was collected and concentrated under reduced pressure. The crude product was purified by column chromatography (50% ethyl acetate in hexanes, $R_f = 0.21$) as a yellow oil (190 mg, 26% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.32-7.24 (m, 5H), 3.80 (d, $J = 12.6$ Hz, 1H), 3.74 (dd, $J = 8.4, 8.4$ Hz, 1H), 3.63 (s, 3H), 3.58 (d, $J = 12.6$ Hz, 1H), 3.32 (dd, $J = 8.0, 8.0$ Hz, 1H), 2.94 (ddd, $J = 17.4, 7.8, 7.8$ Hz, 1H), 2.37 (ddd, $J = 18.5, 9.2, 9.2$ Hz, 1H), 2.21 (ddd, $J = 17.0, 8.0, 8.0$ Hz, 1H). Spectral data matched those previously reported.¹⁴⁹

(*N*-Benzylazetidin-2-yl)methanol (92d**)**

LiAlH_4 (70 mg, 1.85 mmol) was added to ester **107** (190 mg, 0.93 mmol) in dry THF (2.5 mL, 0.38 M) at 0 $^\circ\text{C}$ under nitrogen atmosphere. The reaction was warmed up to rt over 1 h. The consumption of the alcohol as observed on TLC, the reaction was then quenched with distilled water (0.5 mL), followed by the addition of 1 M NaOH (0.5 mL), diluted with THF (5 mL), and 100 mg Mg_2SO_4 , stirred for 15 min. The suspension was

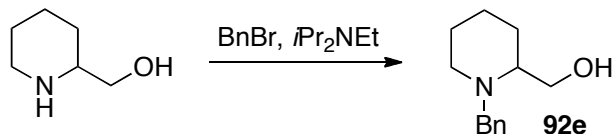
filtered, washed several times with THF, the resulting filtrate was collected and concentrated under reduced pressure. The alcohol **92d** was purified by column chromatography (20% methanol in dichloromethane, $R_f = 0.25$) as a yellow oil (119 mg, 74% yield). **FTIR** ν_{\max} (cm^{-1}): 3397, 3086, 3063, 3028, 2997, 2946, 2925, 2835, 1495, 1453, 1044, 1029, 735, 699; **^1H NMR** (500 MHz, CDCl_3) δ 7.32-7.25 (m 5H), 3.68 (d, $J = 12.7$ Hz, 1H), 3.58 (d, $J = 12.7$ Hz, 1H), 3.42 (dd, $J = 7.7$ Hz, 1H), 3.35-3.28 (m, 3H), 3.08-3.01 (br s, 1H), 2.94 (ddd, $J = 7.6, 7.6, 7.6$ Hz, 1H), 2.21 (dddd, $J = 6.3, 6.3, 6.3, 6.3$ Hz, 1H), 1.96-1.90 (m, 1H); **^{13}C NMR** (125 MHz, CDCl_3) δ 138.0, 128.8, 128.5, 127.4, 67.0, 62.4, 62.0, 51.5, 18.8; **HRMS** (EI^+) m/z calc for $\text{C}_{11}\text{H}_{15}\text{NO}$ $[\text{M}]^+$: 177.1154, found: 177.1154.

***N*-Benzylazetidine-2-carbaldehyde (**93d**)**



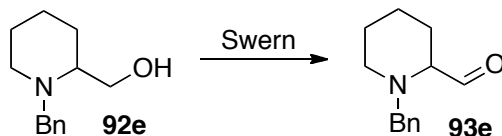
The aldehyde **93d** was synthesized by a Swern oxidation to furnish the product as a yellow oil (33 mg, 62% yield). **FTIR** ν_{\max} (cm^{-1}): 3086, 3-62, 3028, 3003, 2959, 2929, 2843, 1725, 1495, 1453, 1364, 1298, 1238, 1150, 1068, 1029, 986, 795, 737, 701; **^1H NMR** (500 MHz, CDCl_3) δ 9.41 (d, $J = 2.8$ Hz, 1H), 7.32-7.24 (m, 5H), 3.73 (d, $J = 12.4$ Hz, 1H), 3.63 (ddd, $J = 8.5, 2.9$ Hz, 1H), 3.60 (d, $J = 12.5$ Hz, 1H), 3.44 (ddd, $J = 8.8, 2.3$ Hz, 1H), 3.11 (ddd, $J = 8.6, 8.6$ Hz, 1H), 2.29-2.23 (m, 1H), 2.21-2.16 (m, 1H); **^{13}C NMR** (125 MHz, CDCl_3) δ 202.7, 137.3, 129.2, 128.7, 127.8, 71.0, 62.9, 52.3, 19.5; **HRMS** (EI^+) m/z calcd for $\text{C}_{11}\text{H}_{13}\text{NO}$ $[\text{M}]^+$: 175.0997, found: 175.0996.

(*N*-Benzylpiperidin-2-yl)methanol (92e**)**



BnBr (346 μ L, 2.91 mmol) was added to amino alcohol (305 mg, 2.65 mmol) and *i*Pr₂NEt (1.38 mL, 7.94 mmol) in dry toluene (2.6 mL, 1M) at 0 °C under nitrogen. The reaction was warmed up to rt and stirred for 24 h. The reaction was quenched with sat. NaHCO_{3(aq)}, extracted with EtOAc (3 \times 10mL), the combined organic extracts were dried over Na₂SO₄, then concentrated under reduced pressure. The crude product was purified by column chromatography (100 % EtOAc, R_f = 0.30) to furnish the **92e** as a colorless oil (359 mg, 66% yield). **FTIR** ν_{max} (cm⁻¹): 3406, 3085, 3062, 3027, 2933, 2856, 2795, 1494, 1452, 1410, 1370, 1338, 1219, 1181, 1061, 1028, 990, 781, 735, 698; **¹H NMR** (500 MHz, CDCl₃) δ 4.07 (d, *J* = 13.4 Hz, 1H), 3.86 (dd, *J* = 10.8, 4.1 Hz, 1H), 3.52 (dd, *J* = 10.7, 3.4 Hz, 1H), 3.31 (d, *J* = 13.4 Hz, 1H), 2.86 (dd, *J* = 11.6, 3.7 Hz, 1H), 2.82-2.75 (br s, 1H), 2.45 (ddd, *J* = 4.1, 4.1 Hz, 1H), 2.16-2.12 (m, 1H), 1.71-1.51 (m, 4H), 1.41-1.32 (m, 2H); **¹³C NMR** (125 MHz, CDCl₃) δ 139.2, 129.0, 128.5, 127.1, 62.5, 61.2, 57.9, 51.0, 27.5, 24.3, 23.6; **HRMS** (CI⁺/NH₃) *m/z* calc for C₁₃H₂₀NO [M+1]⁺: 206.1545, found: 206.1539.

***N*-Benzylpiperidine-2-carbaldehyde (93e)**

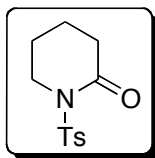


Alcohol **20e** was oxidized using the Swern oxidation conditions to furnish the aldehyde **93e** as a brown oil (35 mg, 79% yield). ¹H NMR (500 MHz, CDCl₃) δ 9.57 (d, *J* = 3.5 Hz, 1H), 7.33-7.30 (m, 5H), 3.76 (d, *J* = 13.5 Hz, 1H), 3.37 (d, *J* = 13.5 Hz, 1H), 2.90 (d, *J* = 11.5 Hz, 1H), 2.82 (d, *J* = 10.3 Hz, 1H), 2.03 (dd, *J* = 11.1, 11.1 Hz, 1H), 1.78-1.73 (m, 1H), 1.66-1.56 (m, 3H), 1.53-1.45 (m, 1H), 1.38-1.29 (m, 1H). Spectral data matched those previously reported.¹⁵⁰

General Procedure for the NHC-Catalyzed Ring Expansion Reaction for the Synthesis of Functionalized Lactams

*i*Pr₂NEt (1 equiv.) was added to the aldehyde (1 equiv.) and triazolium salt **7k** (0.10 equiv.) in dry CH₂Cl₂ in a test tube, at rt, under N₂ atmosphere. The rubber septum, along with the nitrogen line was removed and replaced with a yellow cap. The reaction was stirred at rt until the consumption of the aldehyde was observed by TLC. The reaction mixture was then filtered through a pad of silica, washed with EtOAc. The resulting filtrate was concentrated. No further purification required, unless otherwise stated.

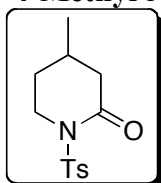
1-Tosylpiperidin-2-one (108a)



Off-white solid (26 mg, 90% yield). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.90 (d, $J = 8.2$ Hz, 2H), 7.31 (d, $J = 8.1$ Hz, 2H), 3.91 (dd, $J = 6.0, 6.0$ Hz, 2H), 2.41 (m, 5H), 1.92-1.87 (m, 2H), 1.79-1.74 (m, 2H). Spectral data matched

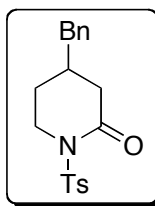
those previously reported.¹⁵¹

4-Methyl-*N*-tosylpiperidin-2-one (108b)



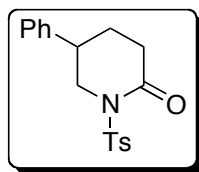
Yellow oil (36 mg, 82% yield). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.90 (d, $J = 8.2$ Hz, 2H), 7.30 (d, $J = 8.0$ Hz, 2H), 4.19-4.16 (m, 1H), 3.65 (ddd, $J = 11.2, 11.2, 4.3$ Hz, 1H), 2.47 (ddd, $J = 17.2, 4.9, 1.9$ Hz, 1H), 2.42 (s, 3H), 2.05-1.98 (m, 2H), 1.95-1.91 (m, 1H), 1.55-1.47 (m, 1H), 0.98 (d, $J = 6.5$ Hz, 3H). Spectral data matched those previously reported.¹⁵²

4-Phenyl-*N*-tosylpiperidin-2-one (108c)



Impure yellow oil, ~90 % purity. $R_f = 0.18$ (30% ethyl acetate in hexanes). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.89 (d, $J = 8.2$ Hz, 2H), 7.31-7.26 (m, 4H), 7.23-7.19 (m, 1H), 7.09 (d, $J = 7.2$ Hz, 2H), 4.19 (dddd, $J = 11.8, 8.4, 5.0, 3.4$ Hz, 1H), 3.57 (dddd, $J = 12.0, 12.0, 12.0, 4.2$ Hz, 1H), 2.61-2.53 (m, 2H), 2.49-2.42 (m, 1H), 2.42 (s, 3H), 2.17-2.00 (m, 4H), 1.56-1.50 (m, 1H).

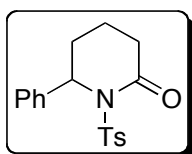
5-Phenyl-*N*-tosylpiperidin-2-one (108d)



Orange oil (39 mg, 83% yield). **FTIR** ν_{max} (cm^{-1}): 3364, 3030, 2950, 1696, 1596, 1494, 1454, 1352, 1242, 1186, 1168, 1125, 1088, 1003,

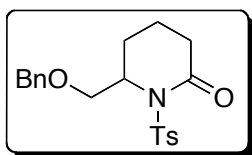
827, 814, 702, 667; **¹H NMR** (500 MHz, CDCl₃) δ 7.92 (d, 8.2 Hz, 2H), 7.38-7.25 (m, 7H), 4.36 (dd, *J* = 6.3, 4.0 Hz, 1H), 3.64 (dd, *J* = 11.4, 11.4 Hz, 1H), 3.17-3.10 (m, 1H), 2.65-2.51 (m, 2H) 2.44 (s, 3H), 2.12-2.07 (m, 1H), 2.06-2.99 (m, 1H); **¹³C NMR** (125 MHz, CDCl₃) δ 169.9, 145.1, 140.8, 136.1, 129.5, 129.1, 129.0, 127.8, 127.2, 52.6, 40.6, 33.9, 27.3, 21.9; **HRMS** (EI⁺) *m/z* calc for C₂₀H₂₃NO₂ [M]⁺: 309.1729, found: 309.1734.

6-Phenyl-*N*-tosylpiperidin-2-one (108e)



Yellow oil (17 mg, 81% yield). **FTIR** ν_{max} (cm⁻¹): 2953, 1693, 1597, 1494, 1453, 1351, 1169, 1087, 814, 702 cm⁻¹; **¹H NMR** (500 MHz, CDCl₃) δ 7.67 (dd, *J* = 8.2 Hz, 2H), 7.32-7.28 (m, 3H), 7.16 (d, *J* = 8.2 Hz, 2H), 7.12-7.07 (m, 2H), 5.82 (dd, *J* = 4.5, 4.5 Hz, 1H), 2.59-2.54 (m, 2H), 2.38 (s, 3H), 2.24-2.16 (m, 1H), 2.05-2.03 (m, 1H), 1.73-1.61 (m, 2H); **¹³C NMR** (125 MHz, CDCl₃) δ 170.8, 144.8, 140.6, 136.1, 129.7, 128.9, 128.7, 127.8, 126.6, 60.5, 33.8, 31.6, 21.8, 15.9; **HRMS** (EI⁺) *m/z* calc for C₁₈H₂₀NO₃S [M+1]⁺: 330.1164, found: 330.1166.

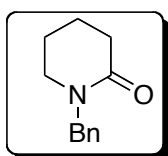
6-(Benzyloxymethyl)-*N*-tosylpiperidin-2-one (108f)



Purified by column chromatography (25% ethyl acetate in hexanes, *R_f* = 0.14) to furnish the desired lactam as a colourless oil (20 mg, 49% yield). **FTIR** ν_{max} (cm⁻¹): 2922, 1696, 1349, 1260, 1164, 1088, 814, 662; **¹H NMR** (500 MHz, CDCl₃) δ 7.89 (d, *J* = 8.3 Hz, 2H), 7.36-7.25 (m, 7H), 4.81-4.77 (m, 1H), 4.52 (ddd, *J* = 23.8, 11.9 11.9 Hz, 2H), 3.74 (dd, *J* = 9.7, 3.6 Hz, 1H), 3.66 (dd, *J* = 9.5, 7.8 Hz 1H), 2.46-2.41 (m, 1H), 2.40 (s, 3H), 2.36-2.29 (m, 1H), 2.23-2.20 (m, 1H), 1.94-1.82 (m, 2H), 1.71-1.66 (m, 1H); **¹³C NMR** (125 MHz, CDCl₃) δ

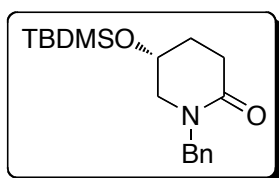
170.9, 144.8, 138.0, 136.8, 129.4, 129.2, 128.7, 128.0, 127.9, 73.6, 71.0, 55.4, 33.7, 25.7, 21.9, 17.0; **HRMS** (EI⁺) *m/z* calc for C₂₀H₂₃NO₂ [M]⁺: 309.1729, found: 309.1734.

***N*-Benzylpiperidin-2-one (111a)**



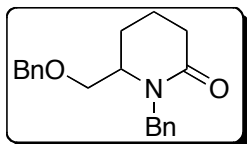
Orange oil (49 mg, 100% yield). **¹H NMR** (500 MHz, CDCl₃) δ 7.33-7.31 (m, 2H), 7.27-7.24 (m, 3H), 4.60 (s, 2H), 3.19 (dd, *J* = 6.1, 6.1 Hz, 2H), 2.47 (dd, *J* = 6.3, 6.3 Hz, 2H), 1.83-1.75 (m, 4H). Spectral data matched those previously reported.¹⁵³

***(R)*-N-Benyl-5-(*tert*-butyldimethylsilyloxy)piperidin-2-one (111b)**



Orange oil (50 mg, 100% yield). **¹H NMR** (500 MHz, CDCl₃) δ 7.30-7.29 (m, 2H), 7.23-7.05 (m, 3H), 4.83 (d, *J* = 14.9 Hz, 1H), 4.34 (d, *J* = 14.9 Hz, 1H), 4.09-4.05 (m, 1H), 3.29 (dd, *J* = 12.4, 3.5 Hz, 1H), 3.10 (ddd, *J* = 12.2, 5.1, 2.4 Hz, 1H), 2.73 (ddd, *J* = 17.0, 9.5, 7.0 Hz, 1H), 2.42 (ddd, *J* = 17.5, 5.5, 5.5 Hz, 1H), 1.92-1.84 (m, 2H), 0.84 (s, 9H), -0.03 (s, 3H), -0.04 (s, 3H). Spectral data matched those previously reported.¹⁵⁴

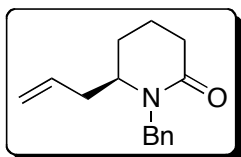
***N*-Benzyl-6-(benzyloxymethyl)piperidin-2-one (111c)**



Yellow oil (19 mg, 49% yield). **FTIR** ν_{max} (cm⁻¹): 3062, 3029, 2944, 2867, 1641, 1495, 1465, 1452, 1414, 1358, 1328, 1260, 1180, 1162, 1096, 1073, 1029, 699; **¹H NMR** (500 MHz, CDCl₃) δ 7.37-7.34 (m, 2H), 7.32-7.28 (m, 5H), 7.25-7.22 (m, 1H), 7.20-7.18 (m, 2H), 5.28 (d, *J* = 15.1 Hz, 1H), 4.44 (ddd, *J* = 12.0, 12.0, 12.0 Hz, 2H), 4.10 (d, *J* = 15.1 Hz, 1H), 3.55-3.42 (m, 3H), 2.51-2.42 (m,

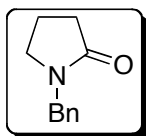
2H), 1.98-1.95 (m, 1H), 1.88-1.86 (m, 1H), 1.76-1.71 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.9, 138.0, 138.0, 128.7, 128.7, 128.0, 128.0, 127.8, 127.3, 73.4, 70.6, 55.2, 48.4, 32.2, 25.8, 17.9; HRMS (EI^+) m/z calc for $\text{C}_{20}\text{H}_{23}\text{NO}_2$ $[\text{M}]^+$: 309.1729, found: 309.1714.

(*R*)-6-Allyl-*N*-benzylpiperidin-2-one (111d)



Orange oil (28 mg, 93% yield). IR ν_{max} : 3064, 3028, 2947, 1690, 1640, 1516, 1496, 1452, 1416, 1343, 1259, 1159, 1072, 1029, 995, 917, 732, 702 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.33-7.22 (m, 5H), 5.68-5.59 (m, 1H), 5.41 (d, $J = 15.2$ Hz, 1H), 5.11-5.07 (m, 2H), 3.98 (d, $J = 15.2$ Hz, 1H), 3.40-3.29 (m, 1H), 2.50-2.44 (m, 3H), 2.30-2.25 (m, 1H), 1.95-1.85 (m, 1H), 1.78-1.76 (m, 1H), 1.72-1.69 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.6, 137.8, 134.2, 128.8, 127.9, 127.4, 118.4, 55.1, 47.6, 37.0, 32.2, 26.4, 17.3; HRMS (EI^+) m/z calc for $\text{C}_{15}\text{H}_{19}\text{NO}$ $[\text{M}]^+$: 229.1467, found: 229.1459.

***N*-Benzylpyrrolidin-2-one (111e)**



Dark orange oil (30 mg, 100 % yield). ^1H NMR (500 MHz, CDCl_3) δ 7.35-7.23 (m, 5H), 4.45 (s, 2H), 3.26 (t, $J = 7.0$ Hz, 2H), 2.45 (t, $J = 8.0$ Hz, 2H), 2.05-1.96 (m, 2H). Spectral data matched those previously reported.¹⁵⁵

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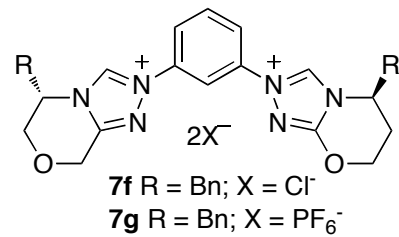
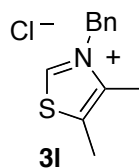
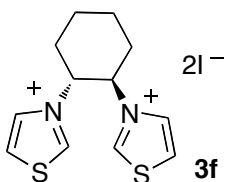
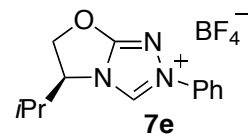
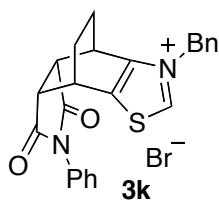
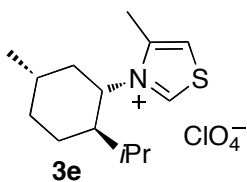
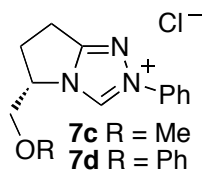
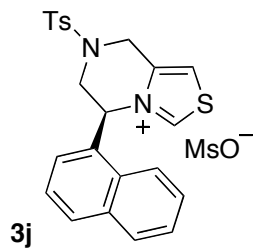
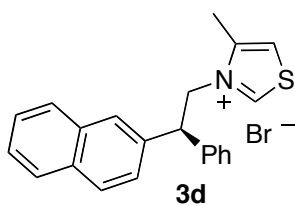
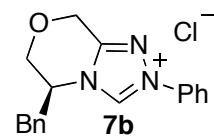
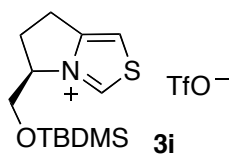
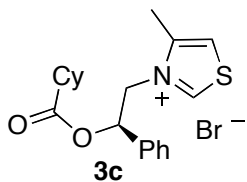
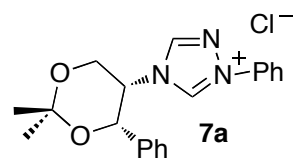
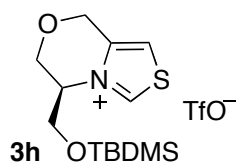
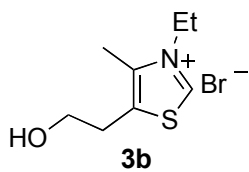
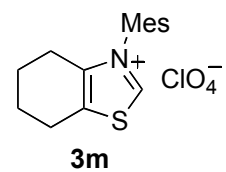
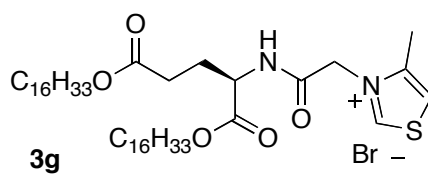
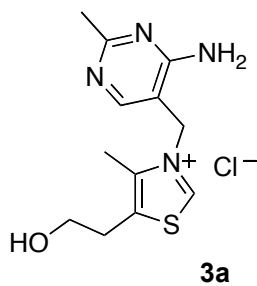
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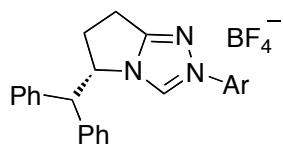
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LIST OF PUBLICATIONS

1. Wang, L.; Thai, K.; Gravel, M.* “NHC-Catalyzed Ring Expansion of Oxacycloalkane-2-carboxaldehydes: A Versatile Synthesis of Lactones”, *Org. Lett.* **2009**, *11*, 891-893.
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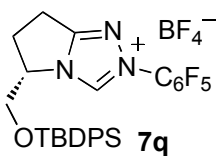
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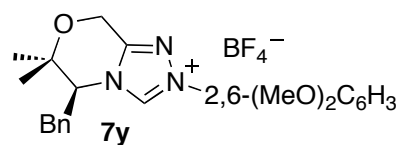


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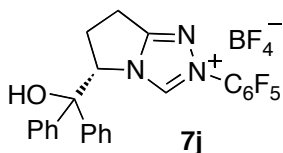
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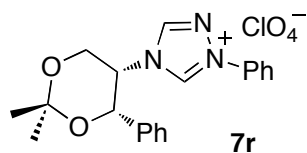
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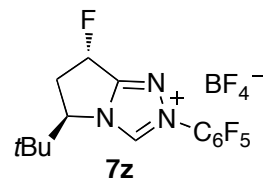
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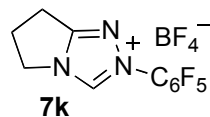
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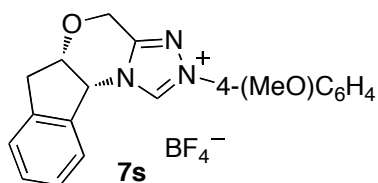
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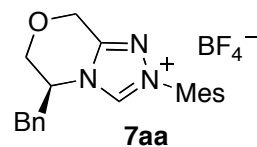
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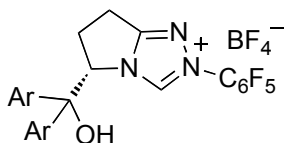
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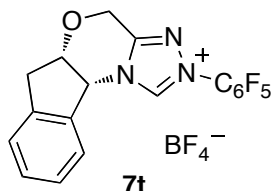
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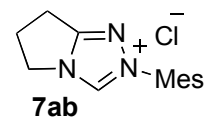
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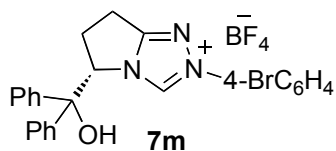
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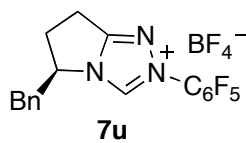
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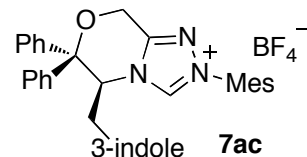
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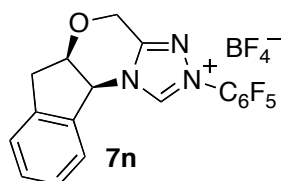
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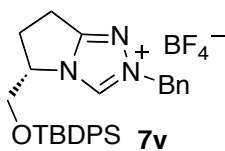
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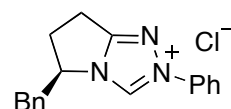
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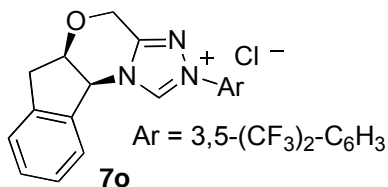
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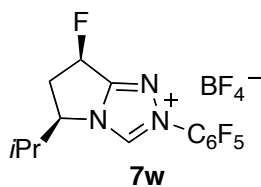
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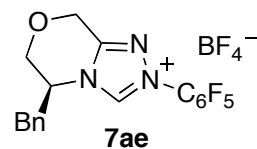
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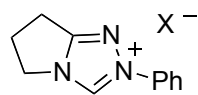
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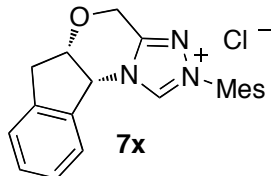


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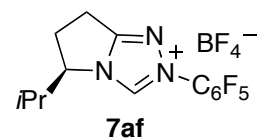


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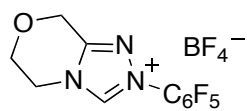
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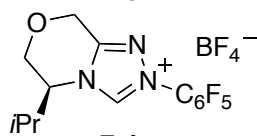
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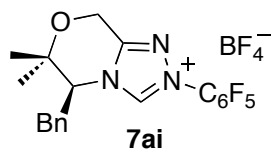
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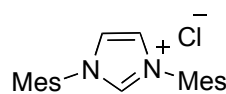
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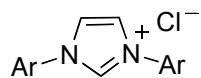
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7ai

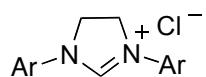


44



86a Ar = 2,4,5-(Me)₃C₆H₂

86b Ar = 2,6-(iPr)₂C₆H₃



87a Ar = 2,4,5-(Me)₃C₆H₂

87b Ar = 2,6-(iPr)₂C₆H₃